BREO® ELLIPTA® 100/25 and 200/25 (Fluticasone furoate / Vilanterol)

Introduction

Katharine Knobil, MD
SVP, Research and Development
GlaxoSmithKline

Impact of Asthma in the US

- Affects an estimated 25.6 million Americans
  - 18.7 M adults[1], 2.6 M adolescents[2], 4.2 M children[2]
- Significant annual healthcare utilization
  - 14.2 million primary care visits,[4] 1.8 million ED visits[5]
  - 439,000 hospital inpatient stays[6]
  - $18 billion attributable to asthma[3]
- Significant patient burden
  - ~50% of patients have uncontrolled asthma when presenting to primary care clinics for non-respiratory reasons[7]
  - 46.7 million days of school, work, or activities missed in the past year[8]

[1] Blackwell et al. NHIS, 2012. Vital Health Stat 2014;10(260):19.
[2] Bloom et al. NHIS, 2012. Vital Health Stat 2013;100(258):7.
[3] Sullivan et al. J Allergy Clin Immunol 2011; Feb;127(2):363-369 .
[4] CDC/NCHS. NAMCS, 2010. Available at http://www.cdc.gov/nchs/fastats/asthma.htm
[5] CDC/NCHS. NHAMCS, 2010. Available at http://www.cdc.gov/nchs/fastats/asthma.htm
[6] CDC/NCHS. NHDS, 2010. Available at http://www.cdc.gov/nchs/fastats/asthma.htm
[7] Mintz et al. Curr Med Res Opin 2009;10:2523-31.
[8] Moorman et al. National Surveillance of Asthma: United States, 2001–2010, Vital Health Stat 2012;3(35):27.

Adherence Affects Outcomes in Asthma

- Poor adherence may contribute to poor outcomes in asthma
- Once daily dosing is associated with higher ICS adherence[1]
  - Increased adherence by ~20 percentage points
  - Doubled proportion of patients >75% adherence
- Improved adherence lowers rates of exacerbations and improves asthma control
  - Every 25% increase in ICS adherence was associated with a ~10% decrease in asthma exacerbations[2]
  - Nearly 1 in 4 exacerbations attributable to poor adherence[2]
- Innovative study ongoing to assess asthma control and adherence in a real world setting[3]

[1] Wells et al. Ann Allergy Asthma Immunol. 2013;111:216-20.
[2] Williams et al. J Allergy Clin Immunol. 2011;128:1185-91.
[3] Woodcock et al. Am J Resp Crit Care Med. 2014;189:A1407

BREO ELLIPTA Once Daily for Asthma

BREO ELLIPTA 100/25

BREO ELLIPTA 200/25

- Vilanterol (VI) 25mcg: long-acting selective beta$_2$-adrenergic agonist (LABA)
- Fluticasone furoate (FF) 100 & 200mcg: long-acting inhaled corticosteroid (ICS)

Approved Medicines Containing FF and VI
All Once Daily Dosing

- ARNUITY ELLIPTA: 20 August 2014
  - FF 100 and 200mcg QD approved for use in asthma in patients ≥12 years of age
- BREO ELLIPTA: 10 May 2013
  - FF/VI 100/25mcg QD approved for use in COPD
- ANORO ELLIPTA: 18 December 2013
  - Umeclidinium (UMEC) 62.5mcg with VI 25mcg QD approved for use in COPD
- VERAMYST (FF): 27 April 2007
  - approved for QD use in perennial and seasonal allergic rhinitis in adults and children ≥2 years of age

Proposed Indication and Dosing

- Indication:
  - *BREO ELLIPTA is a combination ICS/LABA indicated for the once-daily treatment of asthma in patients aged 12 years and older.*
- Dosing:
  - *The recommended starting dosage of BREO ELLIPTA is 100/25 or BREO ELLIPTA 200/25 administered as 1 inhalation once daily.*
  - *The starting dose is based on patients' asthma severity. For patients previously treated with low- to mid-dose corticosteroid-containing treatment, BREO ELLIPTA 100/25 should be considered. For patients previously treated with mid- to high-dose corticosteroid-containing treatment, BREO ELLIPTA 200/25 should be considered.*

Safety of LABAs for the Treatment of Asthma: Class Labeling

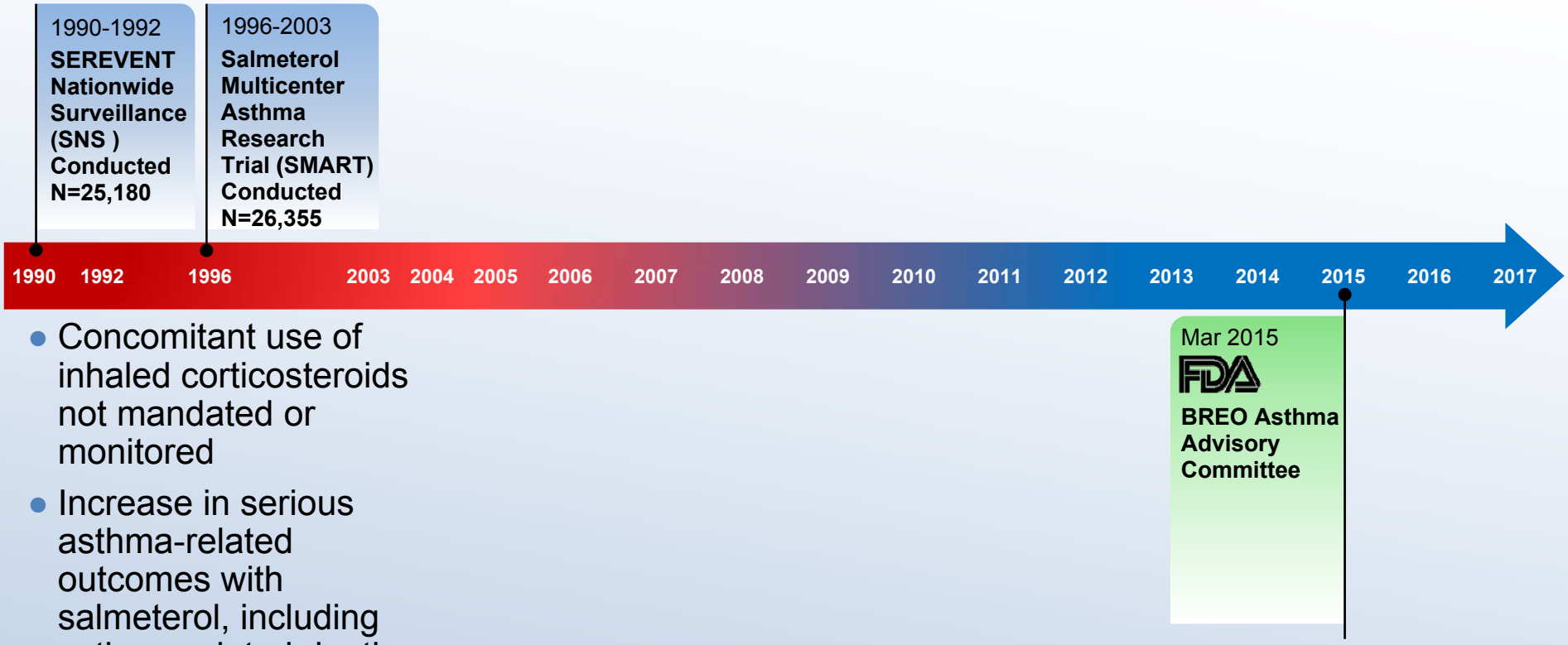
- Boxed warning requirement in the prescribing information for all LABAs for the treatment of asthma
- Early studies of LABAs in patients in asthma in which ICS was either not required or not supplied showed increase risk of serious asthma events

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including vilanterol, an active ingredient in BREO® ELLIPTA®. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Therefore, when treating patients with asthma, physicians should only prescribe BREO ELLIPTA for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO ELLIPTA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use BREO ELLIPTA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids *[see Warnings and Precautions (5.1)]*.

Timeline of LABA-related Discussions



- Concomitant use of inhaled corticosteroids not mandated or monitored
- Increase in serious asthma-related outcomes with salmeterol, including asthma-related death
- Risk of serious asthma-related outcomes was mitigated when patients reported ICS use at baseline

Timeline of LABA-related Discussions

1990-1992
SEREVENT Nationwide Surveillanc (SNS) Conducted N=25,180

1996-2003
Salmeterol

1990 1992

2016 2017

- Concor inhaled not ma monitor
- Increas asthma outcom salmete asthma
- Risk of asthma outcom mitigate patients use at

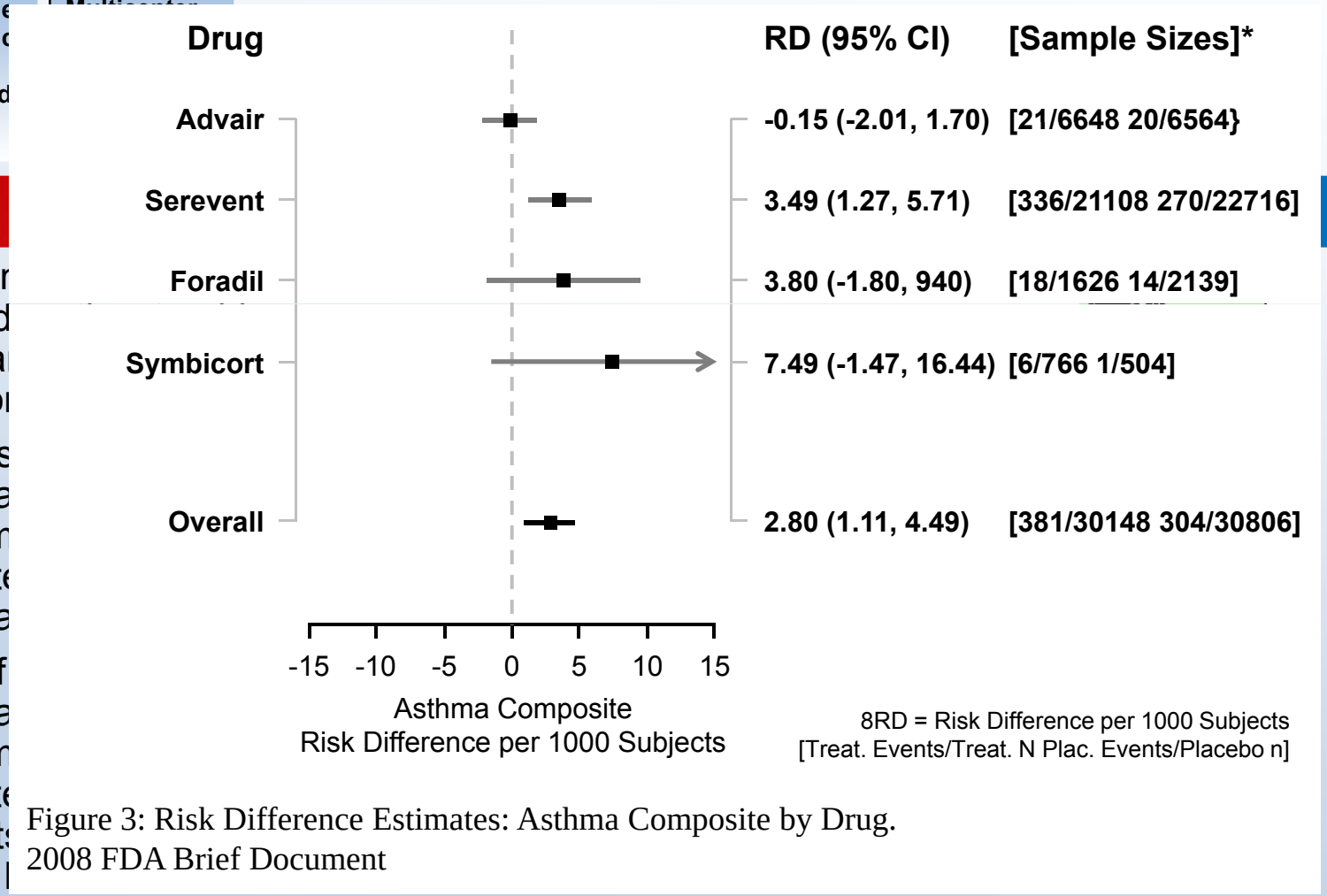
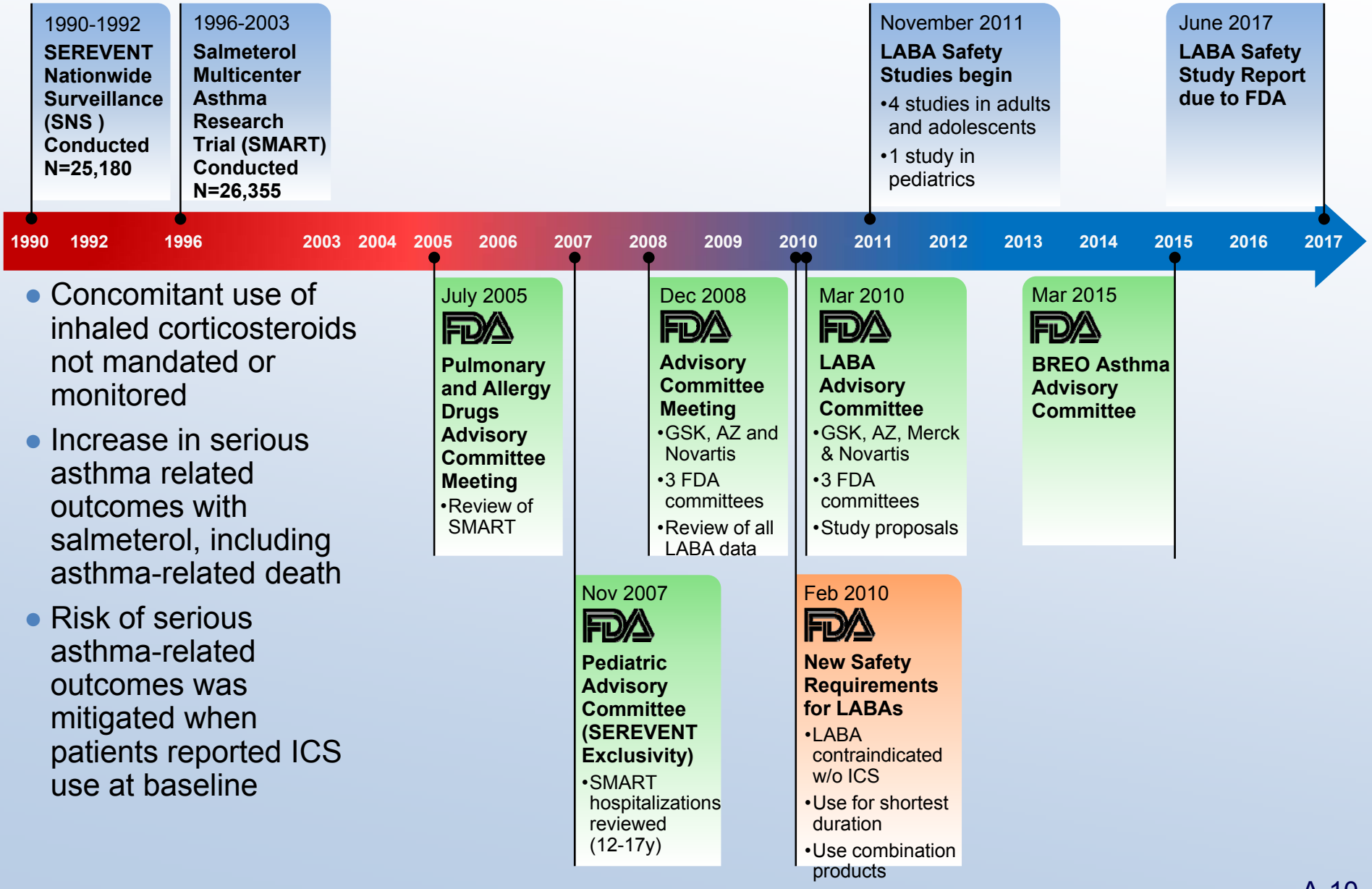


Figure 3: Risk Difference Estimates: Asthma Composite by Drug.
2008 FDA Brief Document

Timeline of LABA-related Discussions



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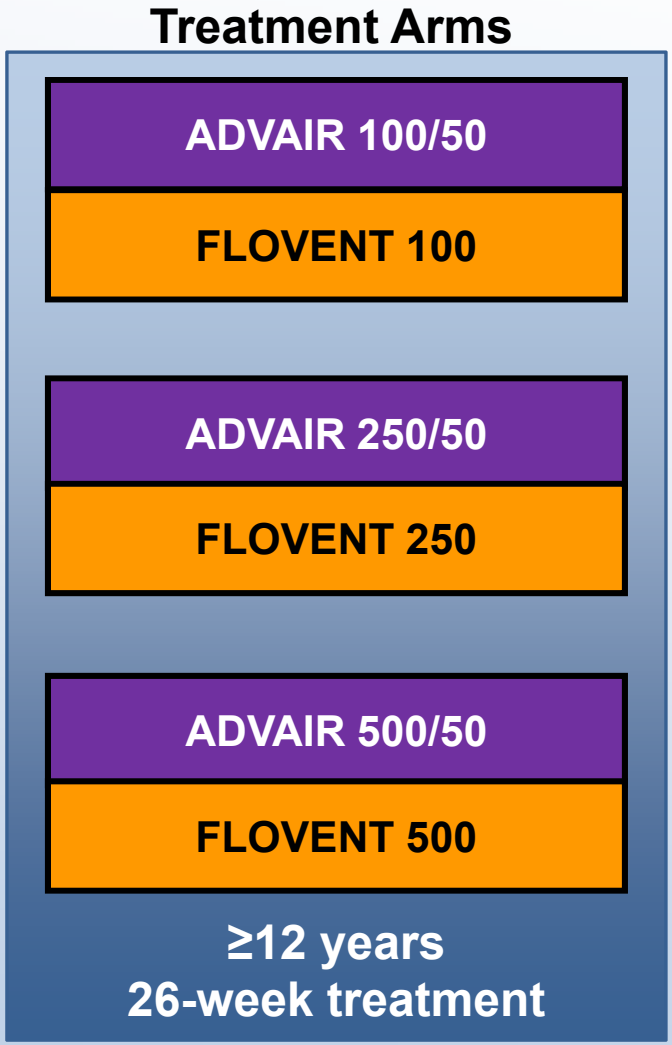
Ongoing LABA Safety Program

- To evaluate whether the addition of a LABA to ICS therapy is non-inferior in the risk of serious asthma-related events vs. ICS alone
- Externally adjudicated composite endpoint of serious asthma-related events including:
  - Hospitalization
  - Endotracheal intubation
  - Death
- Approximately 50,000 subjects to be enrolled across 4 sponsors

Ongoing LABA Safety Program: Adult and Adolescent

(as of December 30, 2014)

- **Adult/adolescent study**
  - N=11,664 planned
  - expected 87 subjects with an event
- 11,724 randomized
  - 1228 adolescents
- 58 subjects have experienced an asthma-related outcome:
  - 58 hospitalizations
  - 2 intubations*
  - 0 deaths

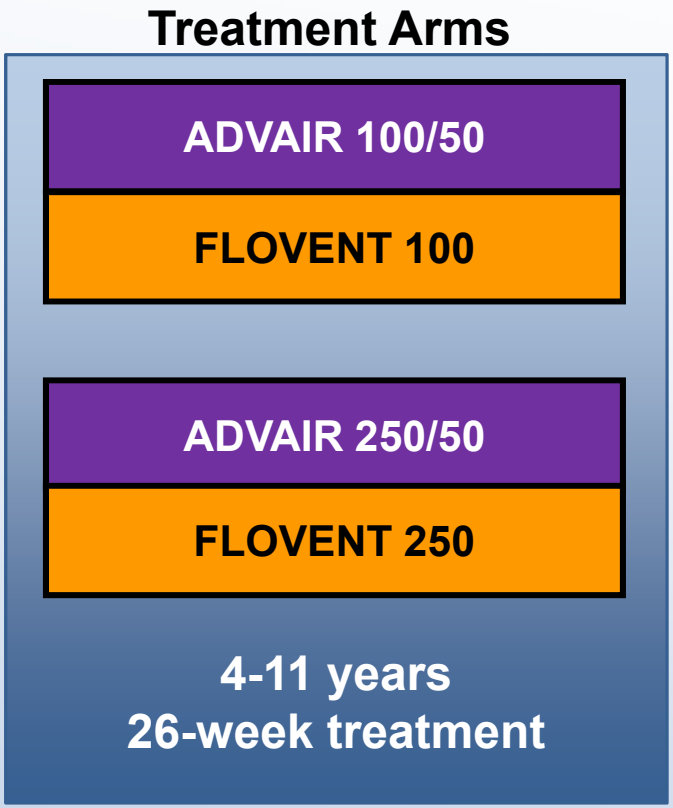


*during hospitalization
SAS115359 available at: https://clinicaltrials.gov/ct2/show/NCT01475721
ADVAIR=fluticasone propionate/salmeterol: FLOVENT=fluticasone propionate

Ongoing LABA Safety Program: Pediatric

(as of December 30, 2014)

- **Pediatric study**
  - N=6,200 planned
  - expected 44 subjects with an event
- 5,602 randomized
- 38 subjects have experienced an asthma-related outcome:
  - 38 hospitalizations
  - 0 intubations
  - 0 deaths



SAS115358 available at: https://clinicaltrials.gov/ct2/show/NCT01462344

ADVAIR=fluticasone propionate/salmeterol: FLOVENT=fluticasone propionate

Topics for Discussion

- Large complex program of over 12,000 adults and adolescents with asthma in Phase II and III
  - Well characterized efficacy and safety profile
- Efficacy profile of BREO ELLIPTA
  - Contribution of VI to the BREO ELLIPTA combination
  - Examination of adolescent subgroup
- Safety profile of BREO ELLIPTA
  - Serious asthma events
- Benefit : risk assessment

Advisors

Eugene Bleecker, MD
Professor and Director, Genomics and Personalized Medicine
Wake Forest School of Medicine
Winston-Salem, NC

H. William Kelly, PharmD
Professor Emeritus, Pediatrics
University of New Mexico Health Sciences Center
Albuquerque, NM

Gary G. Koch, PhD
Professor, Biostatistics
Director, Biometric Consulting Laboratory
University of North Carolina at Chapel Hill

Agenda

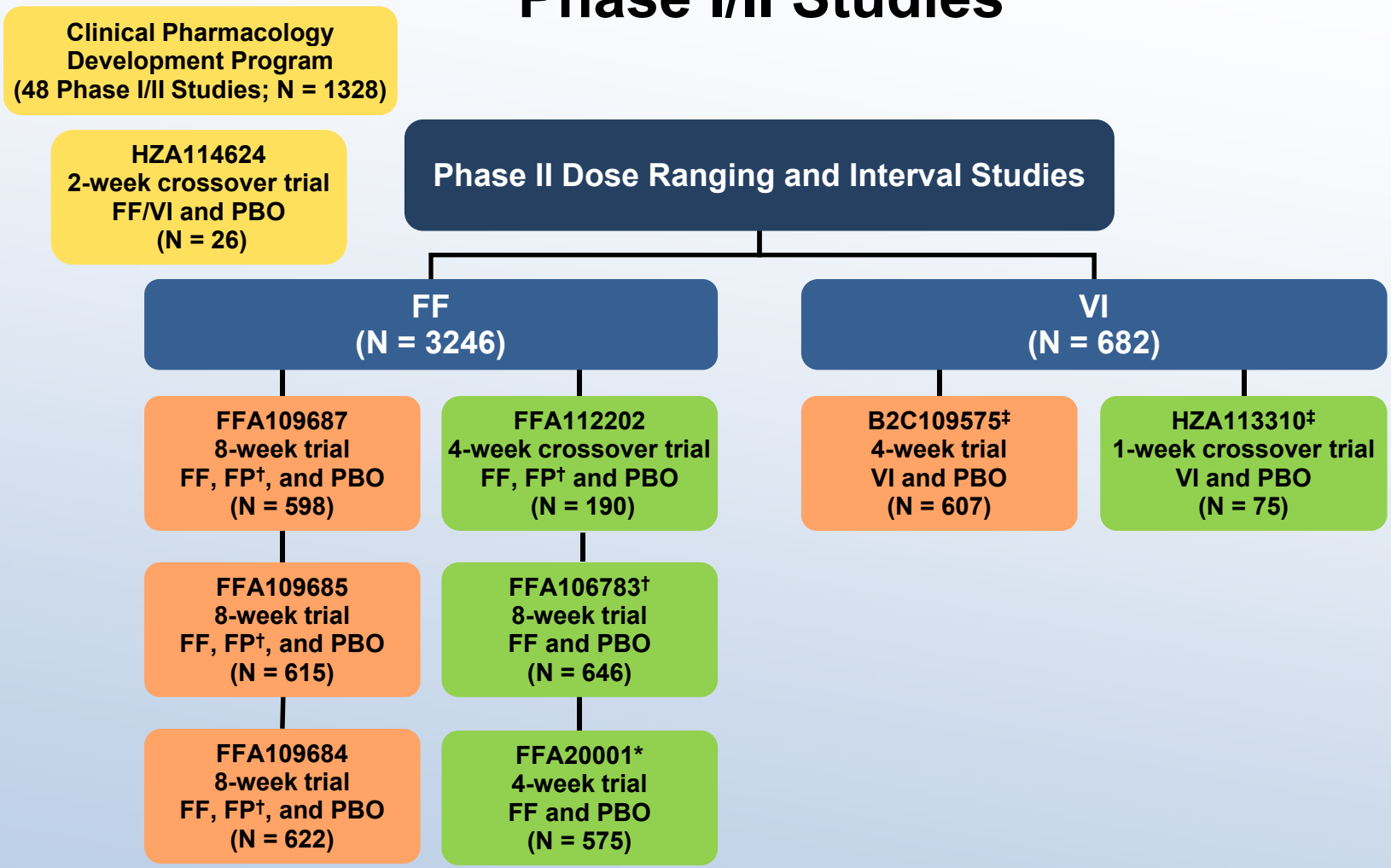
Clinical Efficacy and Safety	**Courtney Crim, MD** Director, Project Physician Lead GlaxoSmithKline
Physician's Perspective	**Eugene Bleecker, MD** Professor and Director, Genomics and Personalized Medicine Wake Forest School of Medicine Winston-Salem, NC
Closing Comments	**Katharine Knobil, MD** Senior Vice President, Research and Development GlaxoSmithKline

BREO ELLIPTA 100/25 and 200/25 (Fluticasone furoate / Vilanterol) Asthma

Efficacy

Courtney Crim, MD
Director of Clinical Development
GlaxoSmithKline

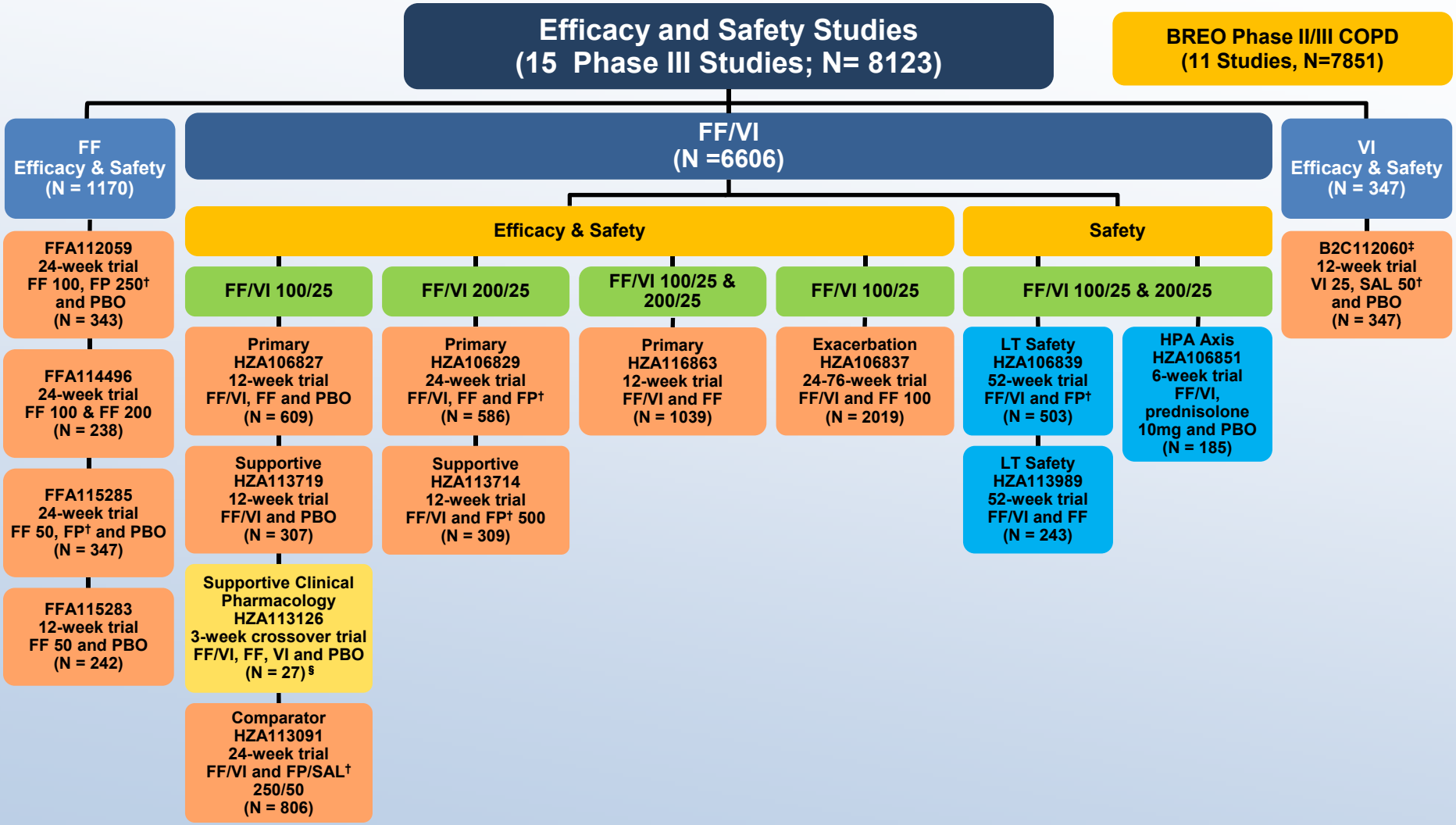
Asthma Clinical Development Program
Phase I/II Studies



FF=fluticasone furoate; FP=fluticasone propionate; PBO=placebo; VI=vilanterol
*administered via Diskhaler
†administered via Diskus
‡subjects continued background ICS

Dose-ranging
Dose interval
Clinical Pharmacology

Asthma Clinical Development Program
Phase III



FF=fluticasone furoate; FP=fluticasone propionate; PBO=placebo; SAL=salmeterol; VI=vilanterol

†administered via Diskus

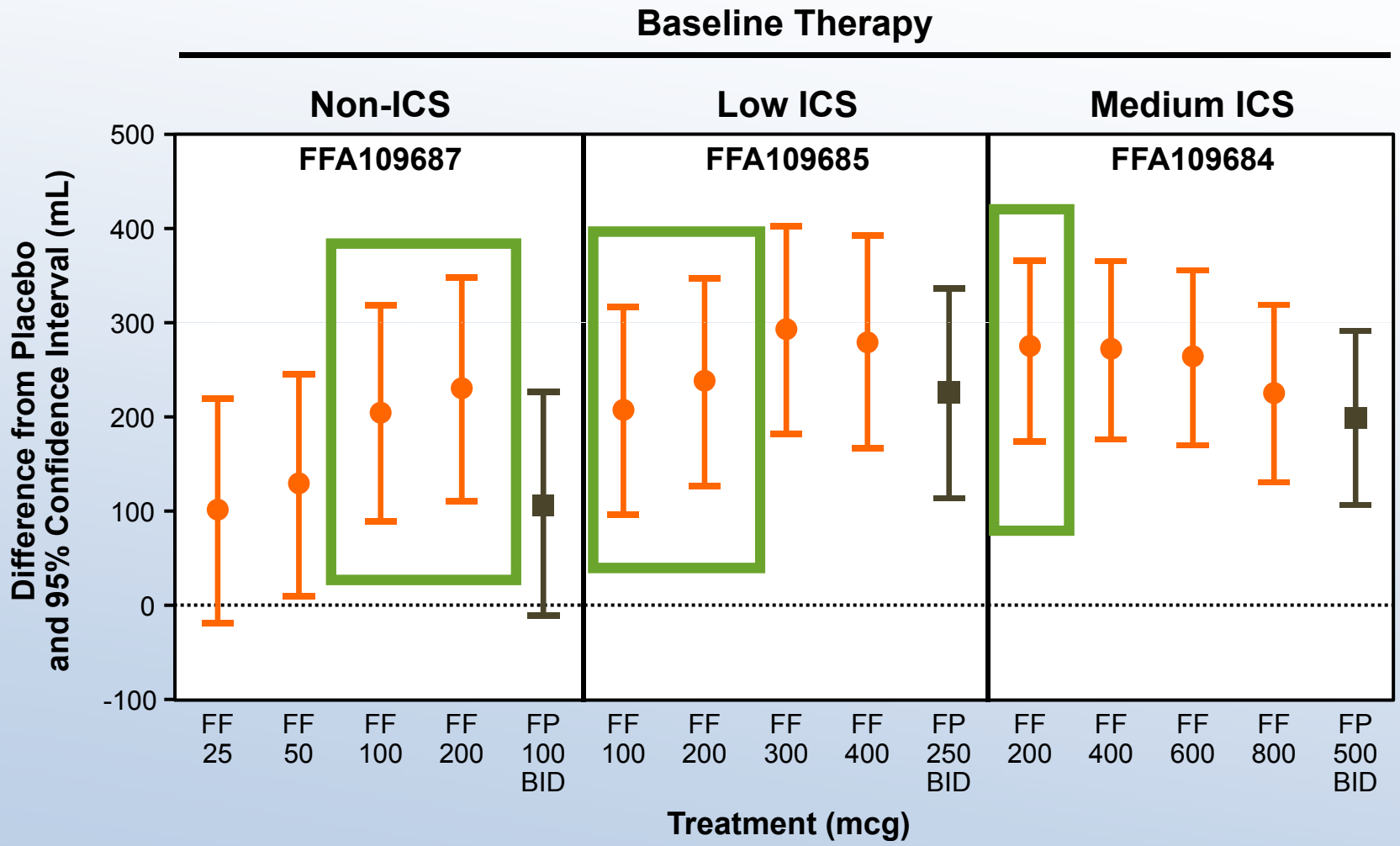
‡subjects continued background ICS

§subjects not included in total N for FF/VI

Efficacy of Fluticasone furoate / Vilanterol

- **Selection of Doses for Phase III**
  - Fluticasone furoate (FF)
  - Vilanterol (VI)
- **Phase III Program for FF/VI**
  - Efficacy of FF monotherapy: FEV_1 trough
  - Efficacy of FF/VI 100/25: FEV_1 trough and WM (0-24 hr)
  - Contribution of VI in the combination: FEV_1 trough and WM (0-24 hr)
  - Clinical benefit of FF/VI 200/25 over 100/25
- **Efficacy Data from Adolescent Sub-population**
- **Efficacy of FF/VI 100/25 QD vs. FP/SAL 250/50 BID**

Phase IIb Asthma Studies Showed a Plateau at FF 200mcg in Trough FEV_1 Response



Last Observation Carried Forward (LOCF)

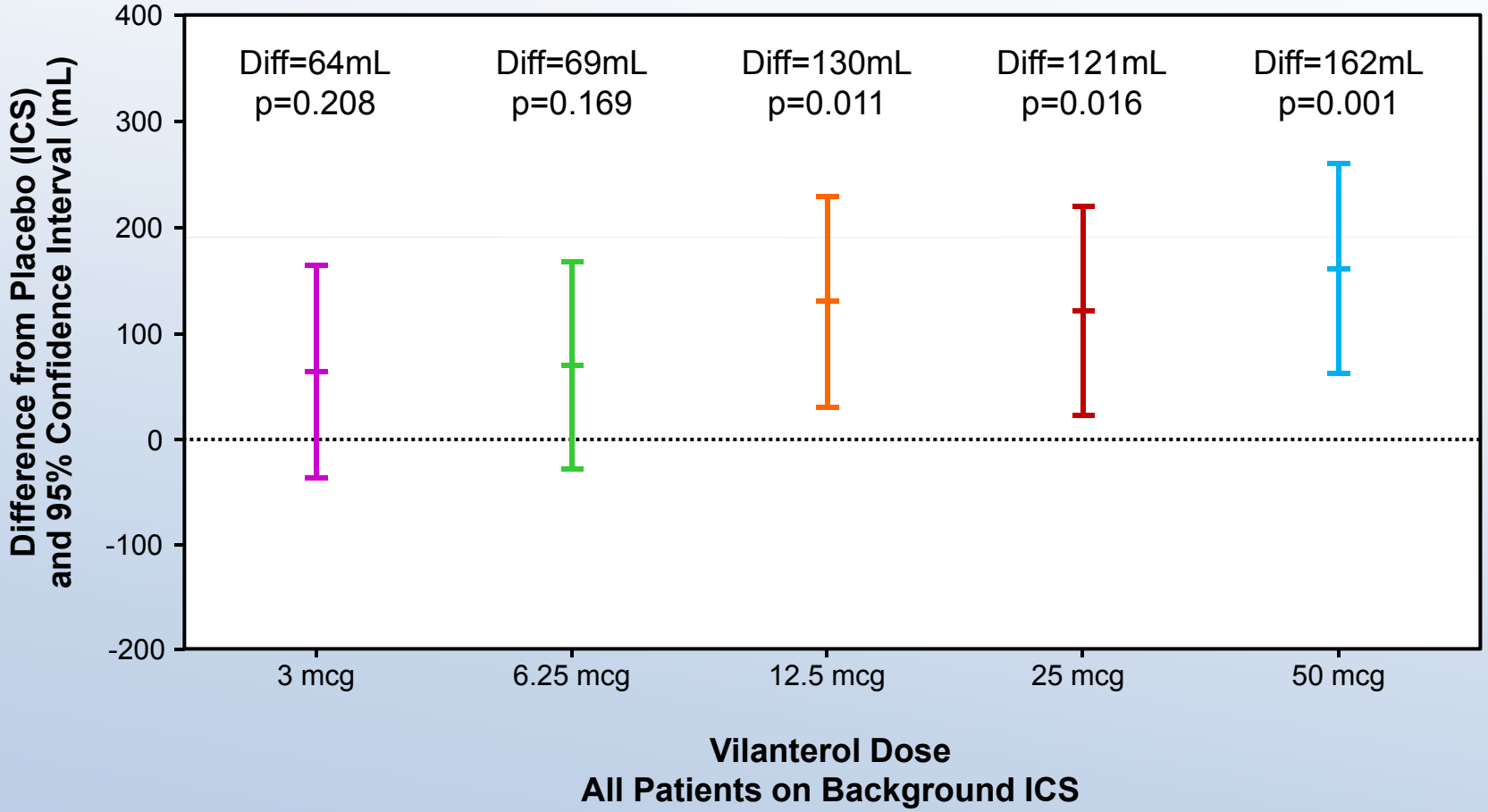
Bateman et al. Respir Med 2012;106:642-50.
Adapted from Bleecker et al. Ann Allergy Asthma Immunol 2012;109:353-58.
Busse et al. Thorax 2012;67:35-41.

Dose Selection of Vilanterol (VI)

- Dose of VI (25mcg) selected for testing in Phase IIIa asthma program was based on a Phase II dose-ranging study in subjects with asthma (Study 575)
  - VI doses of 3, 6.25, 12.5, 25 and 50mcg once daily were evaluated
- Phase II dose-ranging study in COPD also supported 25mcg as appropriate dose of VI to take into Phase III

Lotvall et al. Eur Respir J 2012;40:570-79.

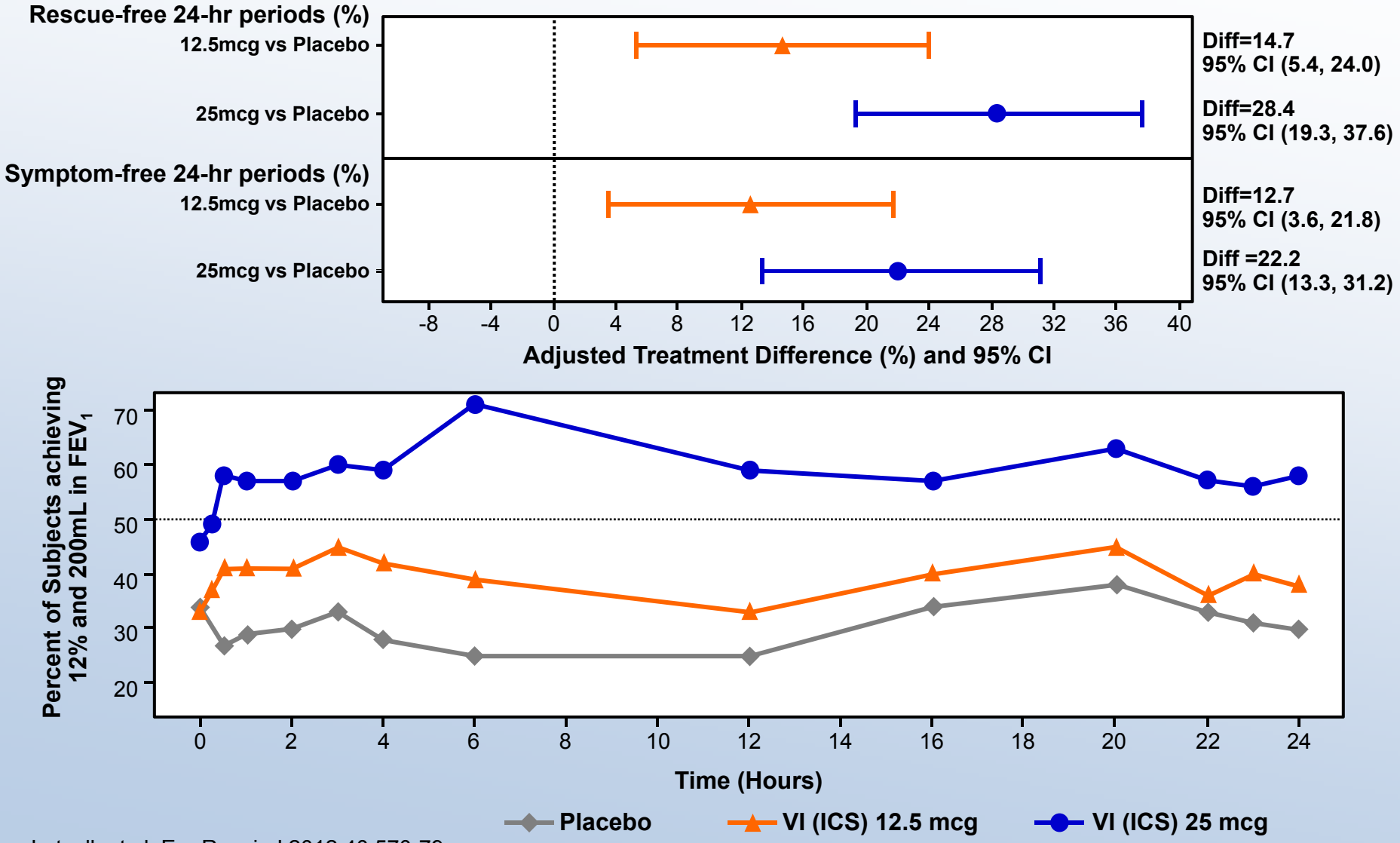
Vilanterol Dose Ranging in Patients with Asthma: 24-hr Trough FEV_1 (Study 575)



Last Observation Carried Forward (LOCF)

Lotvall, et al. Eur Respir J 2012;40:570-79.

Comparative Effects between VI 25mcg and 12.5mcg (Study 575)

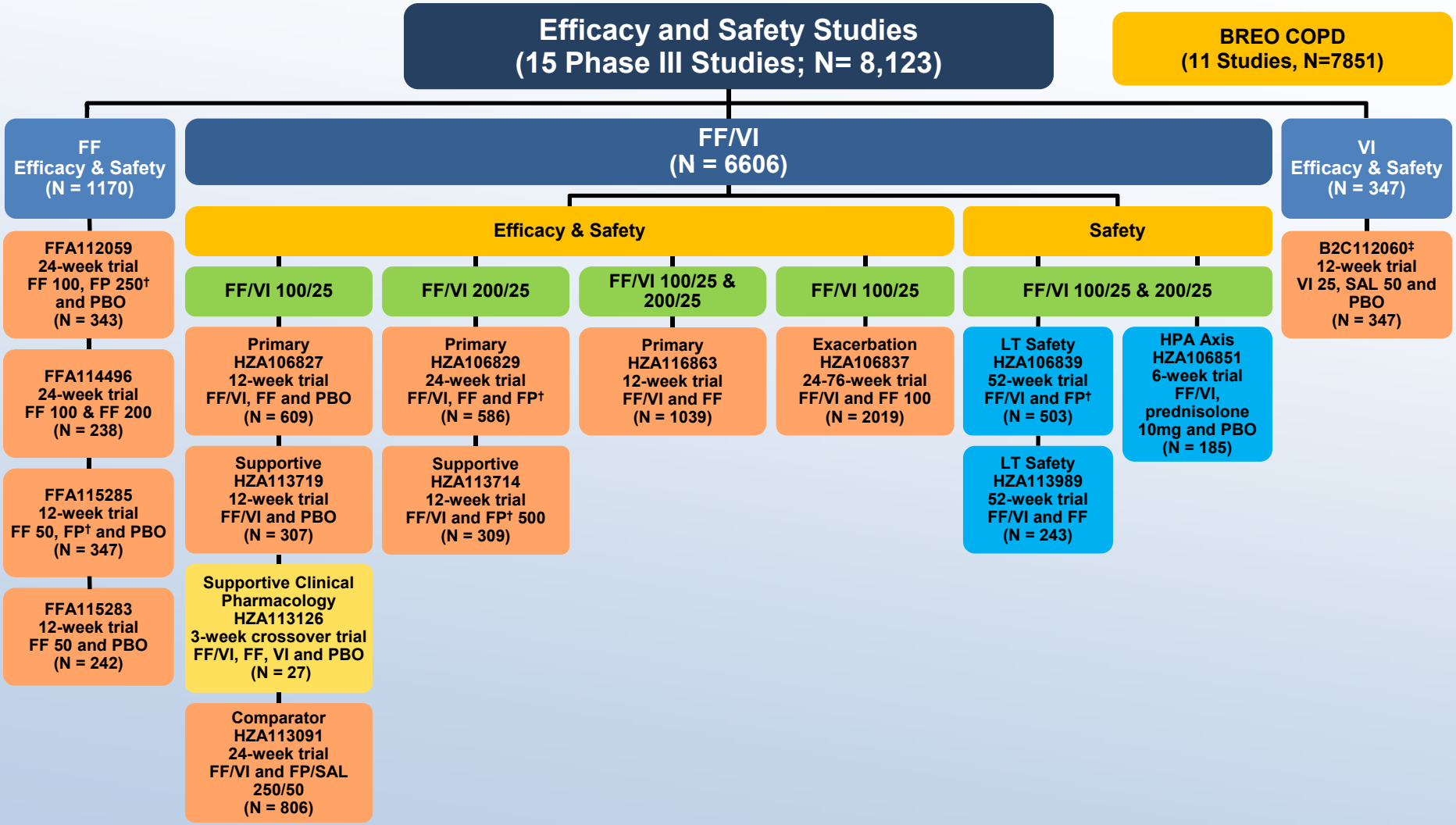


Lotvall, et al. Eur Respir J 2012;40:570-79.

Phase IIb Dosing Conclusions

- FF 100mcg and 200mcg identified as doses to evaluate in Phase III asthma program
- VI 25mcg once daily determined as optimal dose in patients with asthma
- Additional Phase IIb studies comparing once with twice daily dosing confirmed both VI and FF as once daily products

Asthma Clinical Development Program
Phase III



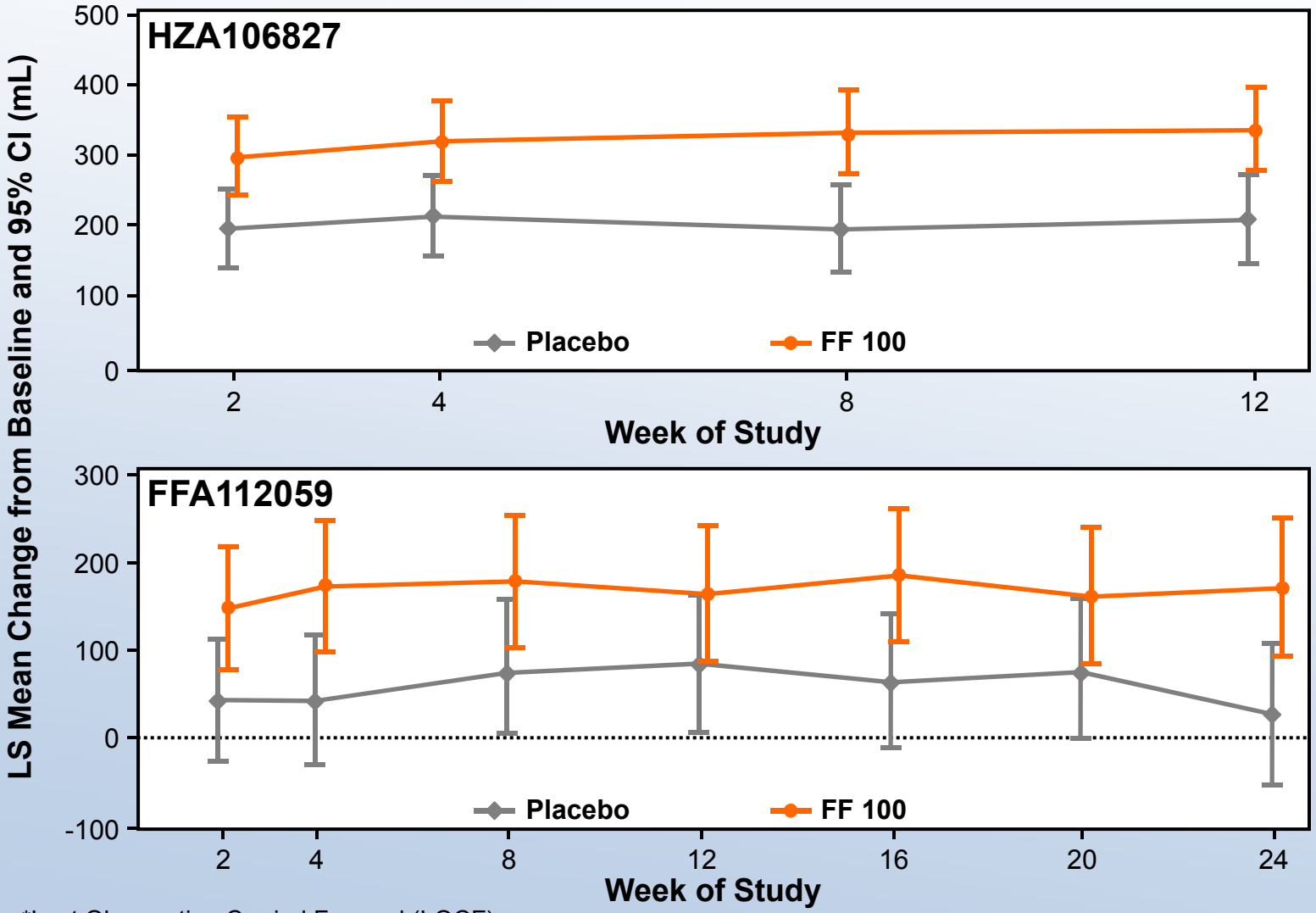
FF=fluticasone furoate; FP=fluticasone propionate; PBO=placebo; SAL=salmeterol; VI=vilanterol
†administered via Diskus
‡subjects continued background ICS

Demographic and Baseline Characteristics (Studies 827, 829 and 863)

	Total (N=2234)	
Age (yrs): Mean (Min-Max) 12-17 yrs, n (%) 18-64 yrs, n (%) ≥65 yrs, n (%)	44.2 (12-84) 170 (8) 1869 (84) 195 (9)	
Female/Male, n (%)	1326 (59) / 908 (41)	
Race, n (%) Caucasian African American/African Heritage Asian Other*	**ITT** 1916 (86) 168 (8) 99 (4) 50 (2)	**US** 400 (68) 166 (28) 12 (2) 9 (2)
Percent Predicted FEV_1 (Screening): Mean (Min-Max)	64.1 (37.0 – 89.6)	
Percent Reversibility: Mean (SD)	29.4 (17.6)	
Absolute Reversibility (mL): Mean (SD)	579.3 (346.6)	

*Includes: American Indian or Alaska Native and Mixed Race

Efficacy of FF
Change from Baseline in Trough FEV_1 (mL)



Diff =136mL*
95% CI (51, 222)
p=0.002

Diff =146mL*
95% CI (36, 257)
p=0.009

*Last Observation Carried Forward (LOCF)

Bleecker, et al. J Allergy Clin Immunol Pract 2014;2:583-61.
Lotvall, et al. Respir Med 2014;108:41-49.

Efficacy of Fluticasone furoate / Vilanterol

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- **Phase III Program for FF/VI**
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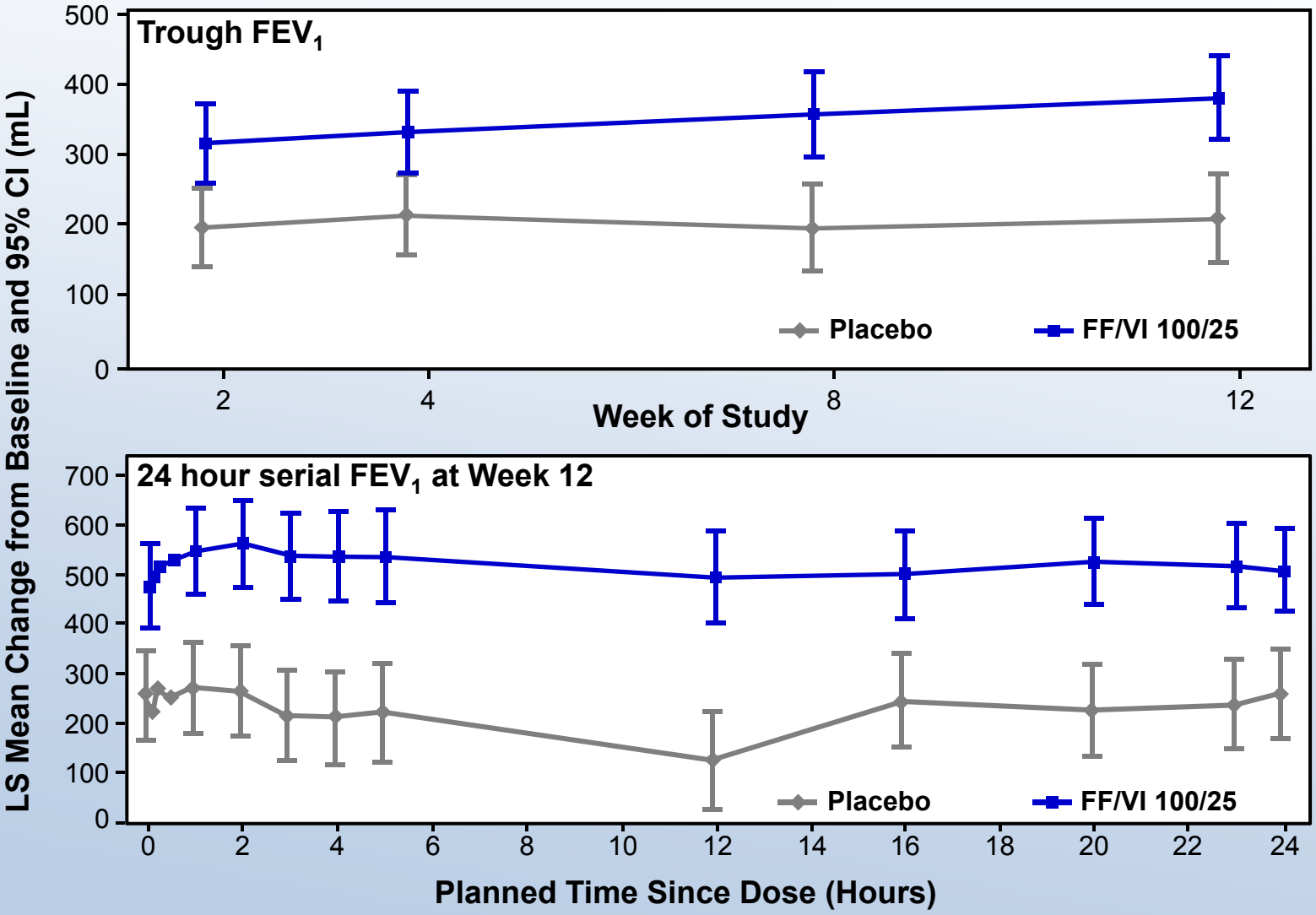
  - **Efficacy of FF/VI 100/25: FEV_1 trough and WM (0-24 hr)**
  - Contribution of VI in the combination: FEV_1 trough and WM (0-24 hr)
  - Clinical benefit of FF/VI 200/25 over 100/25
- **Efficacy Data from Adolescent Sub-population**
- **Efficacy of FF/VI 100/25 QD vs. FP/SAL 250/50 BID**

Efficacy of FF/VI 100/25
Change from Baseline in FEV_1 (mL) (Study 827)

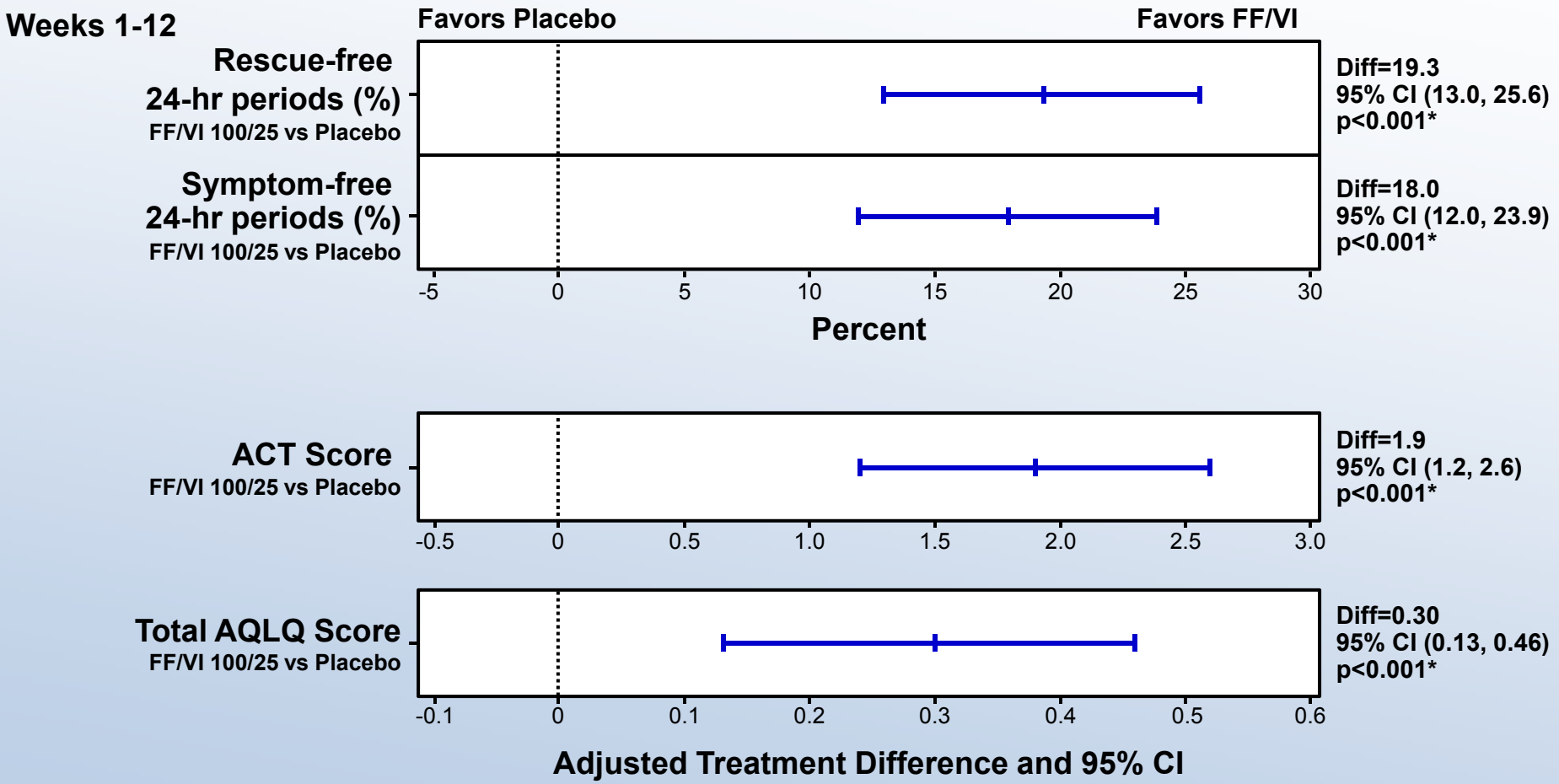


Diff=172mL*
95% CI (87, 258)
p<0.001

*Last Observation Carried Forward (LOCF)

Bleecker, et al. J Allergy Clin Immunol Pract 2014;2:583-61.

FF/VI 100/25 Improves Symptomatic Endpoints (Study 827)



*p value is nominal

Efficacy of Fluticasone furoate / Vilanterol

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  - Clinical benefit of FF/VI 200/25 over 100/25
- **Efficacy Data from Adolescent Sub-population**
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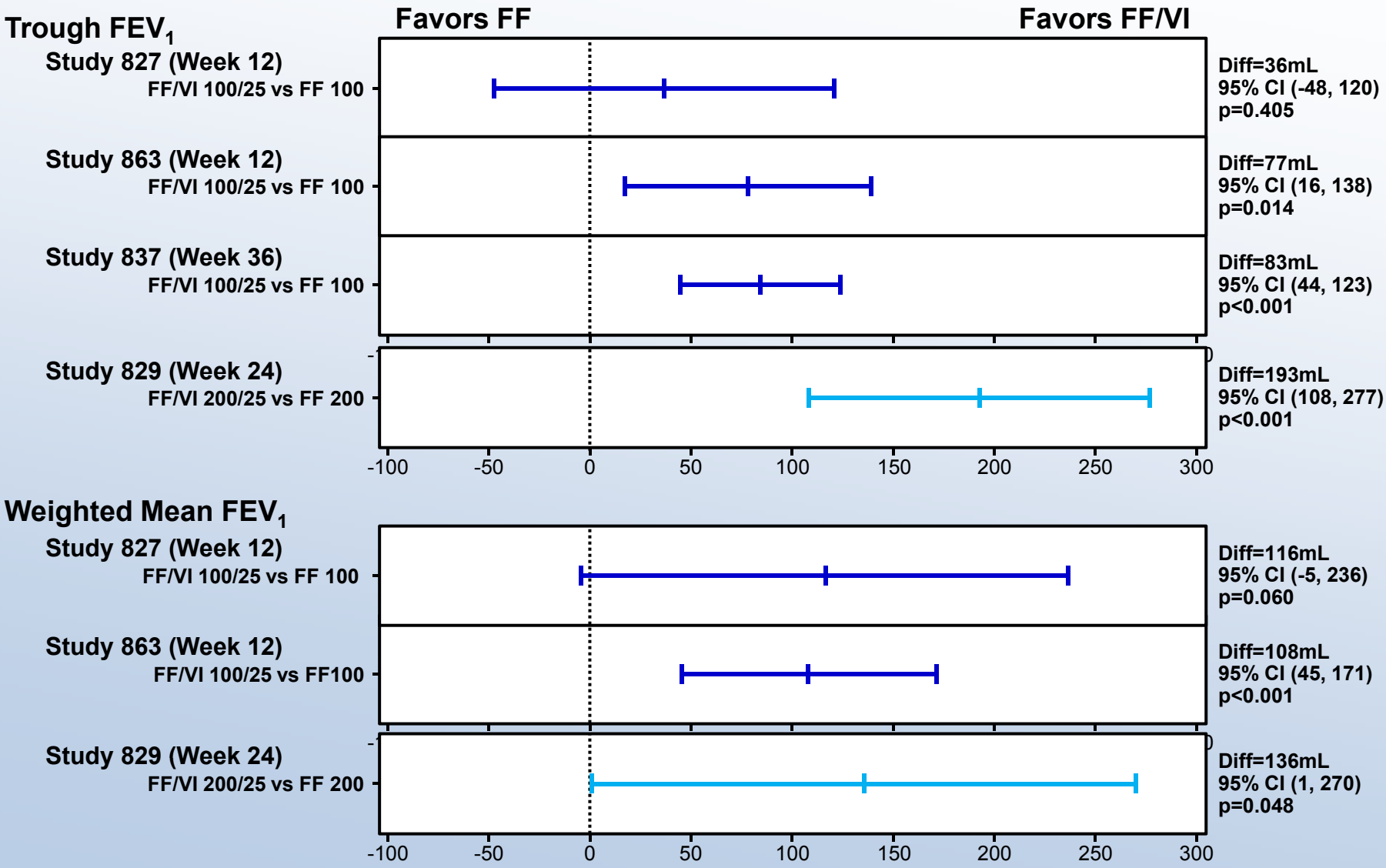
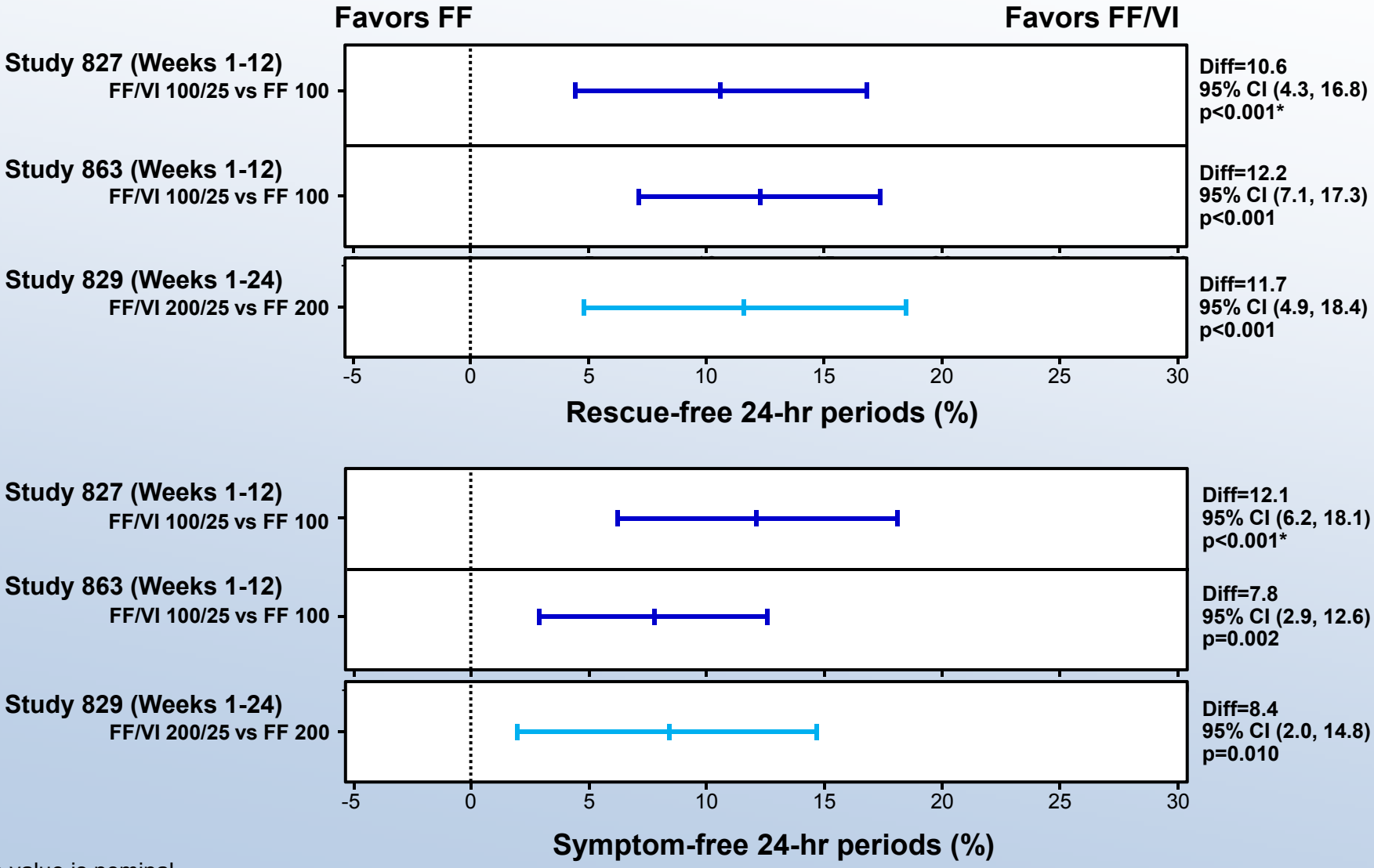
FF/VI vs. FF for Trough and Weighted Mean (0-24 hr) FEV_1 (mL)



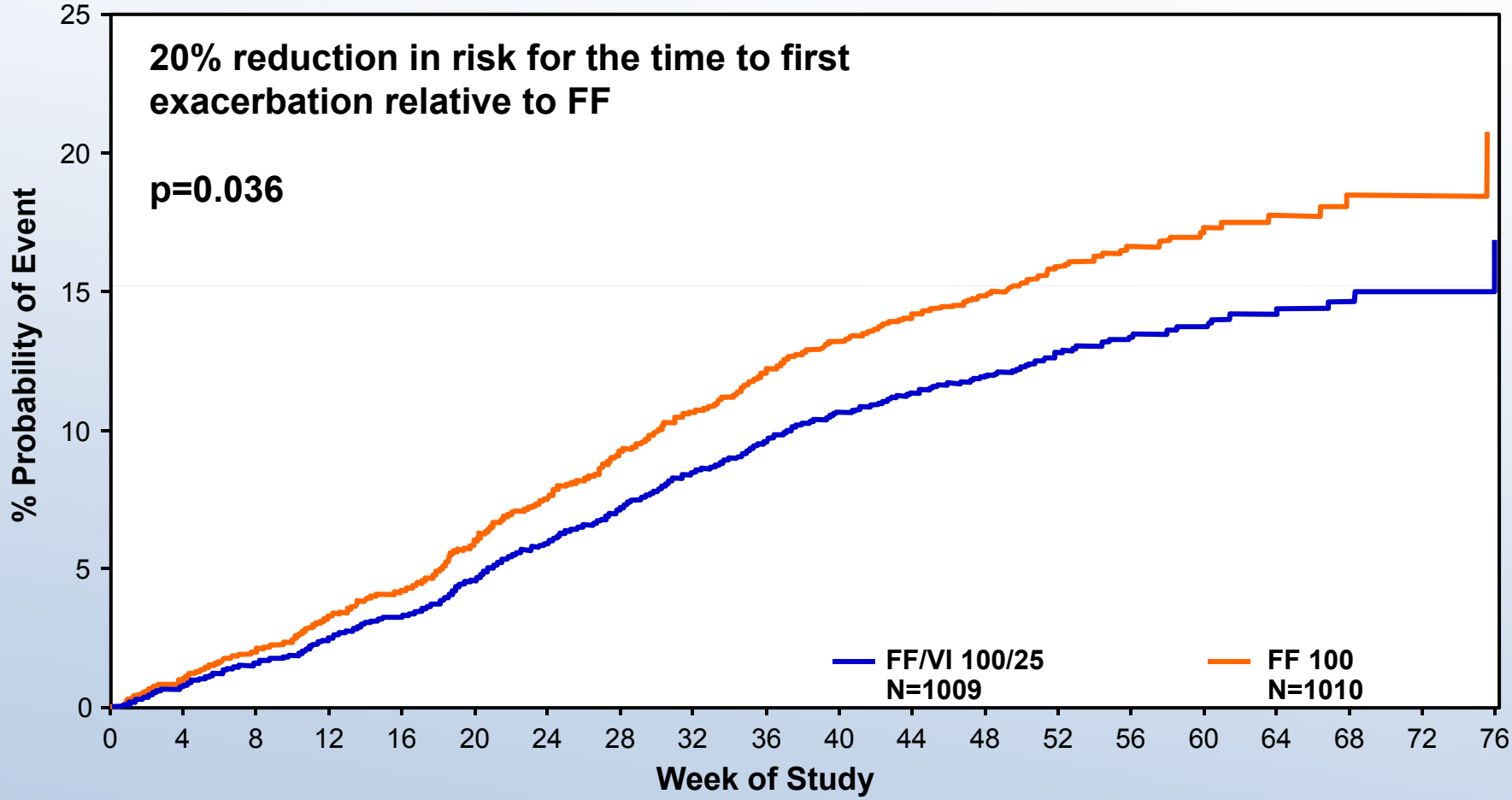
Study 829: O'Byrne, et al. Eur Respir J 2014;43:773-82.

FF/VI vs. FF: Change from Baseline in Rescue- and Symptom-Free 24-Hour Periods



*p value is nominal

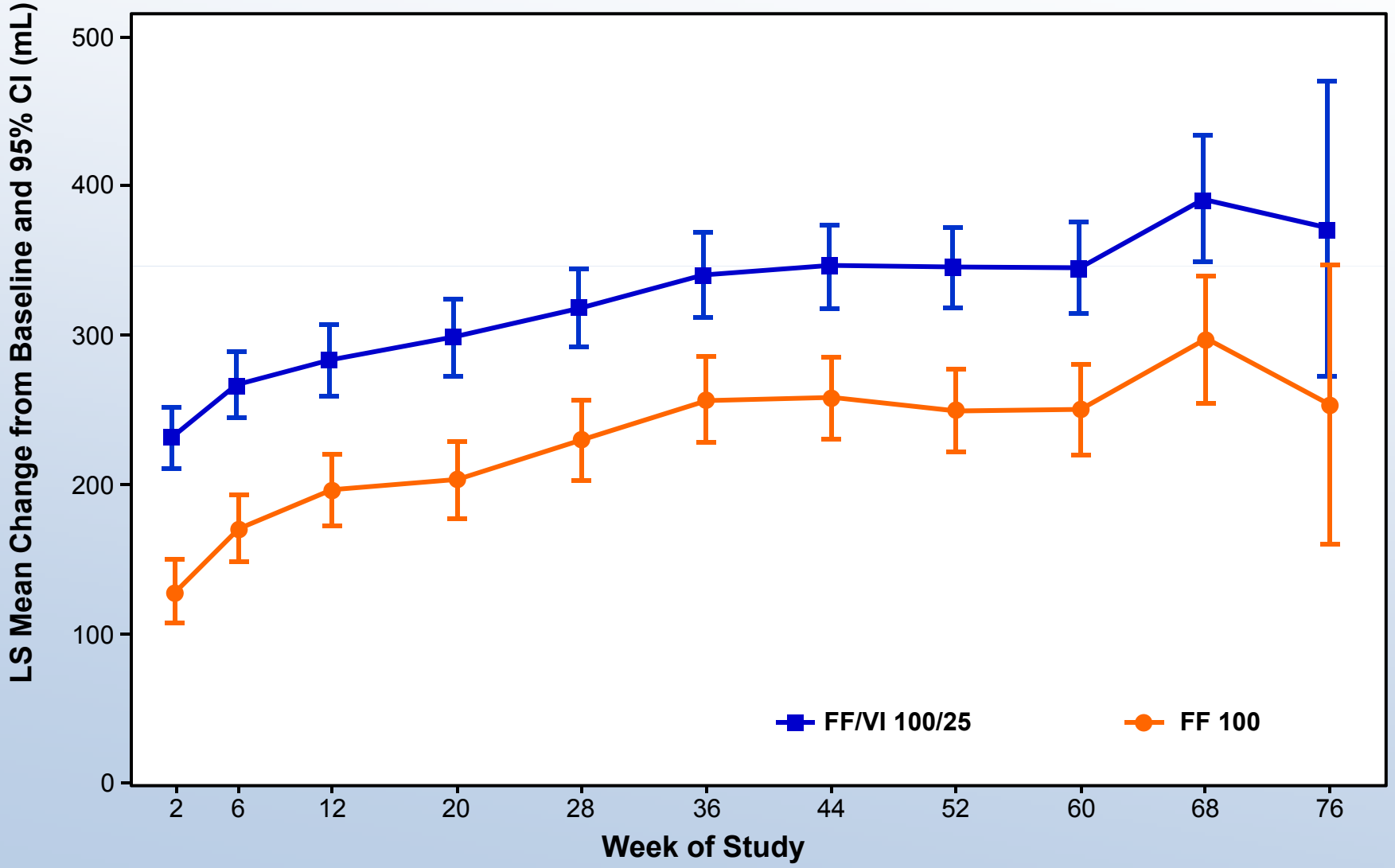
FF/VI Increases Time to First Asthma Exacerbation (Study 837)



ATS/ERS Task Force Definition: Exacerbation defined as one requiring systemic corticosteroids for at least 3 days or an hospitalization/ED visit that required treatment with systemic corticosteroids.

Bateman et al. Thorax 2013;4:312-19.

FF/VI Maintained Improved FEV_1 Compared with FF over the Course of the Study (Study 837)



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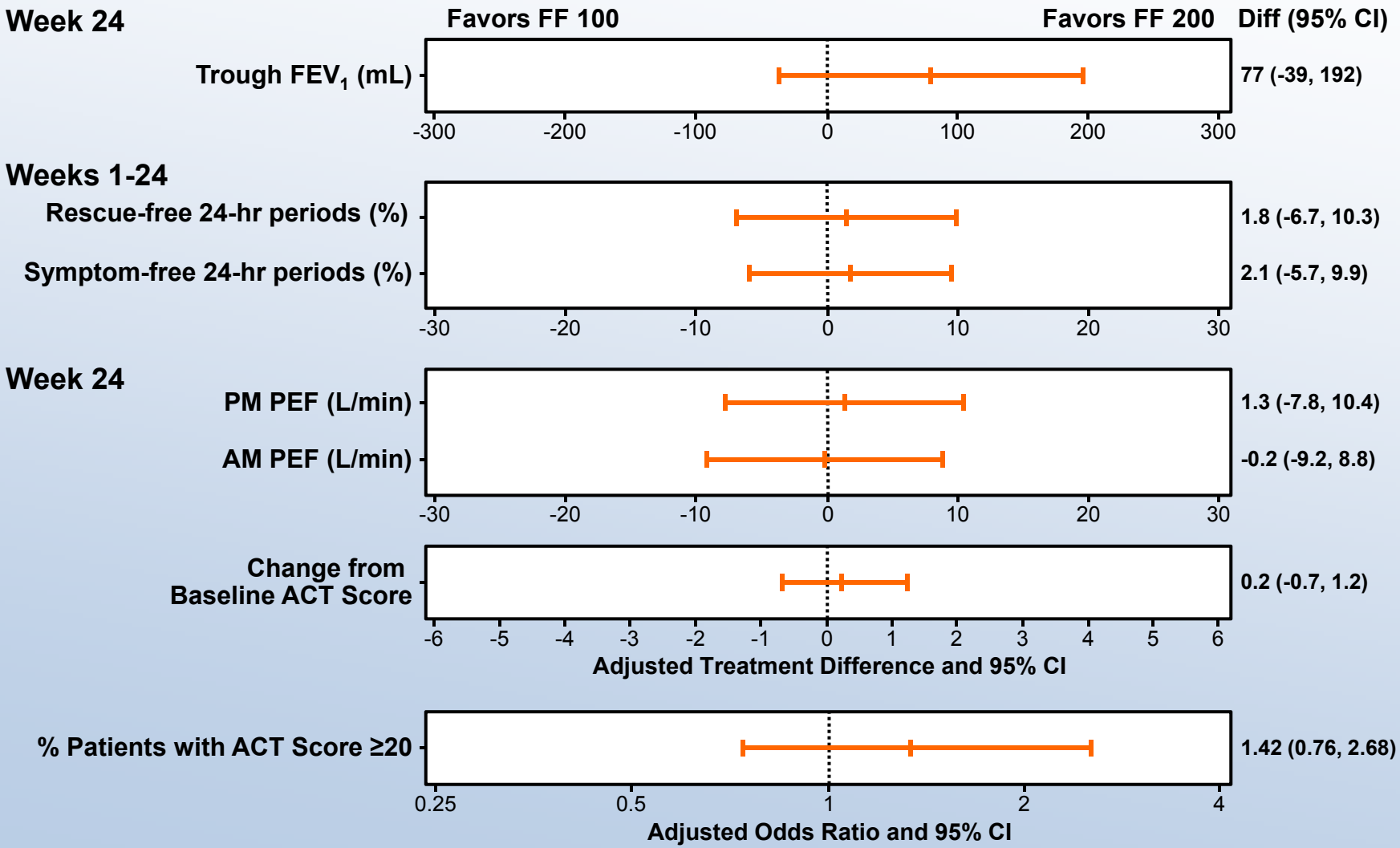
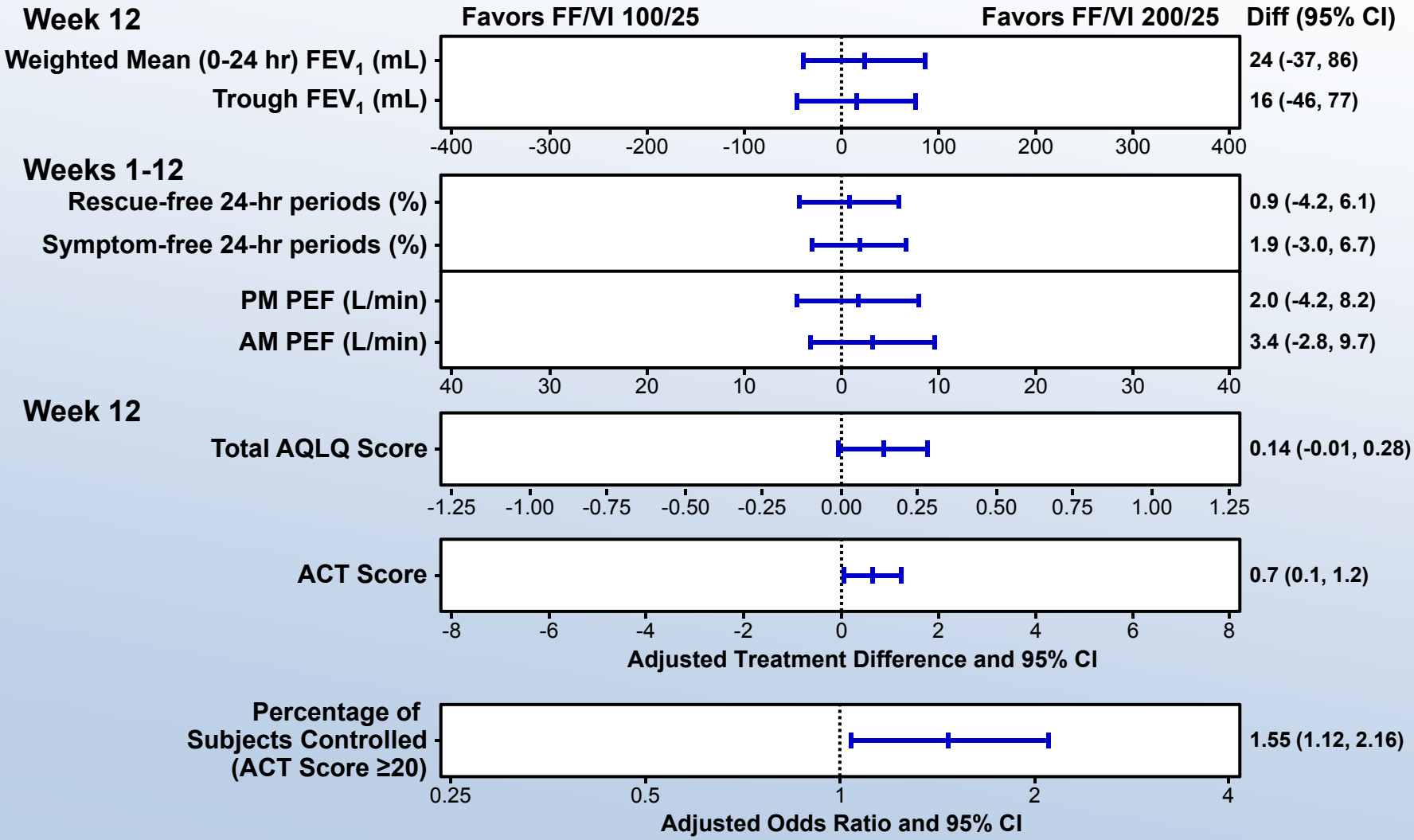
  - **Clinical benefit of FF/VI 200/25 over 100/25**
- **Efficacy Data from Adolescent Sub-population**
- **Efficacy of FF/VI 100/25 compared with FP/SAL 250/50**

Relative Comparison of FF 200 and FF 100 for Efficacy Endpoints (Study 496)



Woodcock et al, BMC Pulm Med 2014;14:113

Relative Comparison of FF/VI 200/25 and FF/VI 100/25 for Efficacy Endpoints (Study 863)



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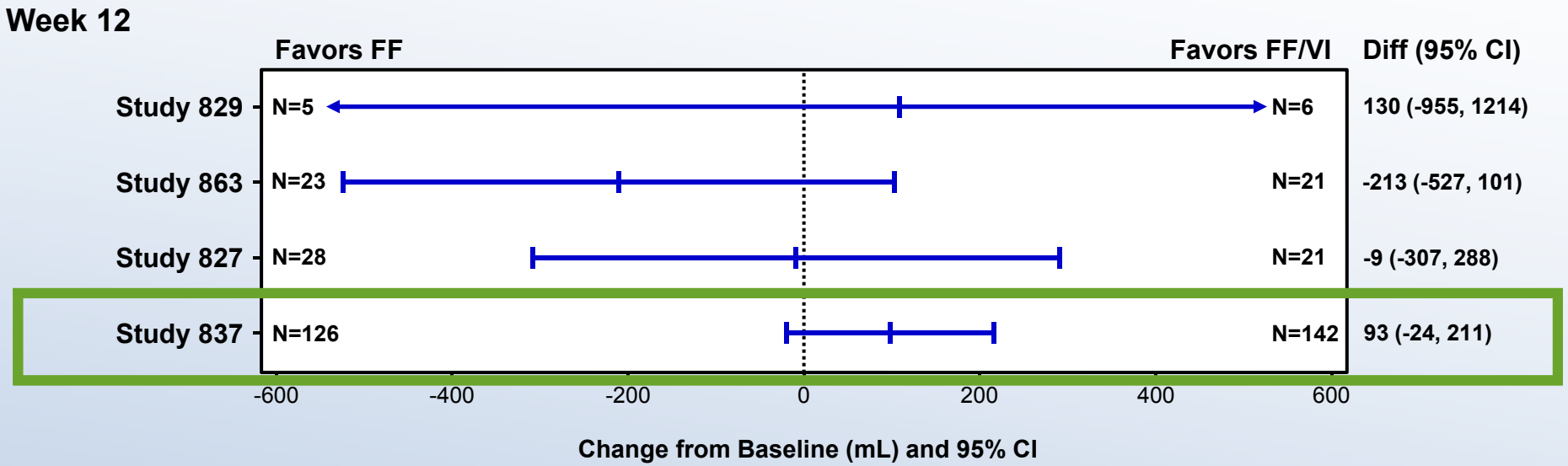
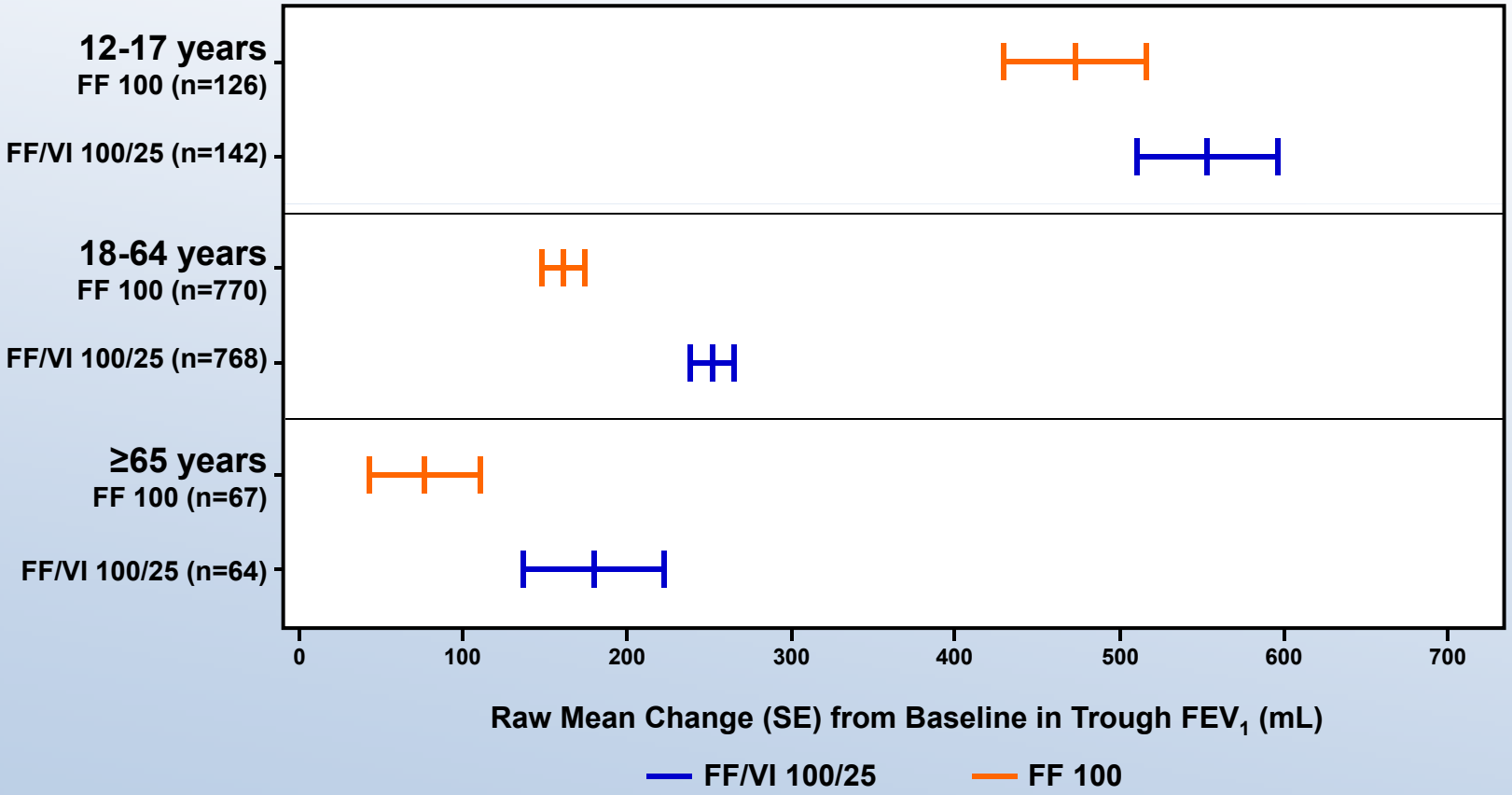
Change from Baseline in Trough FEV_1 in Adolescents



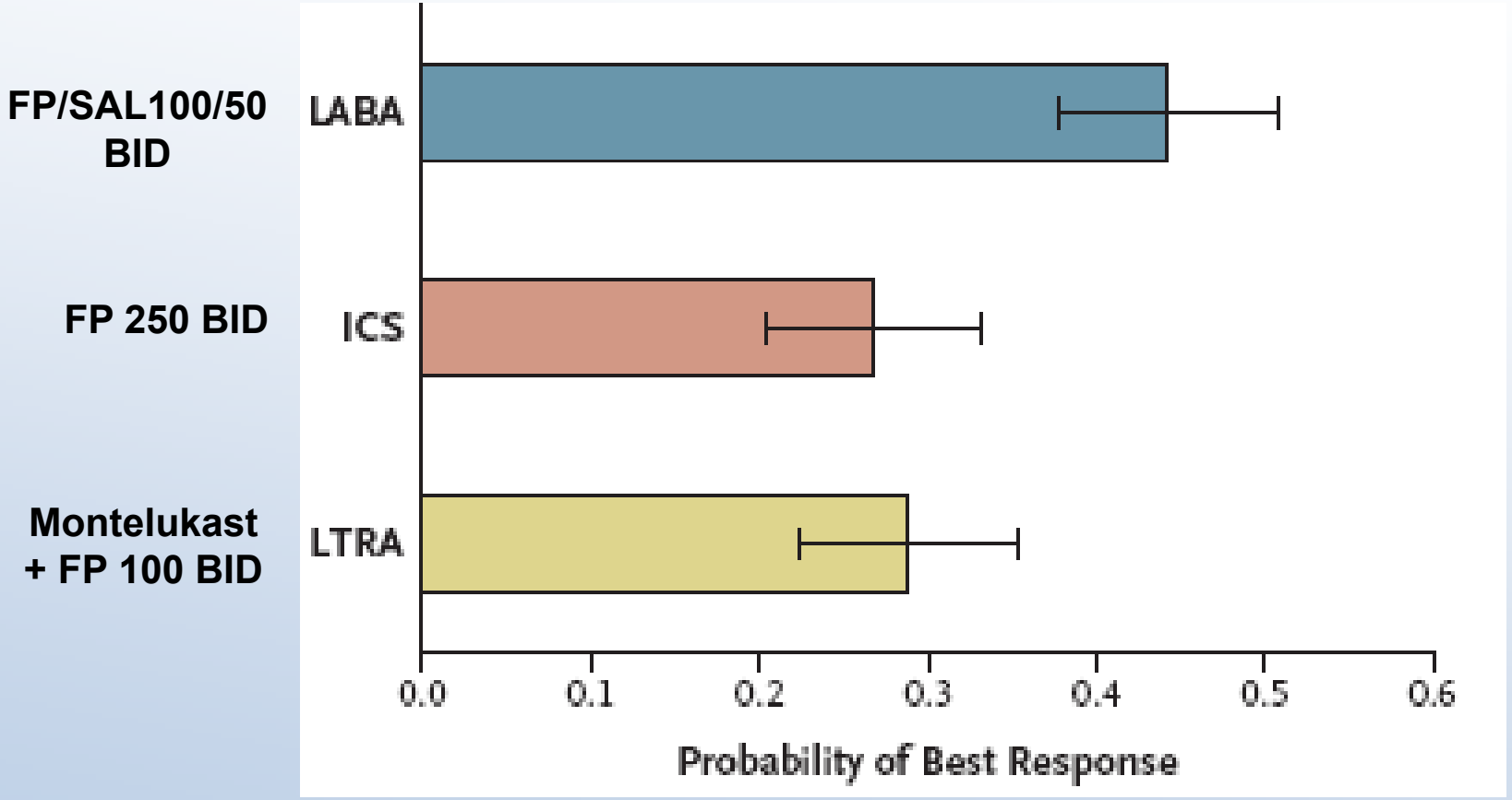
Mean Change from Baseline in Trough FEV_1 (mL) at Week 12 by Age (Study 837)



Rate of Asthma Exacerbations by Age (Study 837)

	ITT Population		12-17 years		≥18 years	
	FF 100 N=1010	FF/VI 100/25 N=1009	FF 100 N=130	FF/VI 100/25 N=151	FF 100 N=880	FF/VI 100/25 N=858
Number (events) of subjects with ≥1 asthma exacerbation	**186 (271)**	**154 (200)**	**9 (10)**	**15 (19)**	**177 (261)**	**139 (181)**
Mean asthma exacerbation rate per subject year	0.19	0.14	0.0008	0.0016	0.2112	0.1514
FF/VI 100/25 vs. FF 100 **Ratio** **95% CI** **p-value**		0.755 (0.603, 0.945) 0.014		1.904 (0.793, 4.573) 0.150		0.717 (0.567, 0.906) 0.005

Probability of Best Response to Step-up Therapies (Children Aged 6-17 Uncontrolled on FP 100 BID)



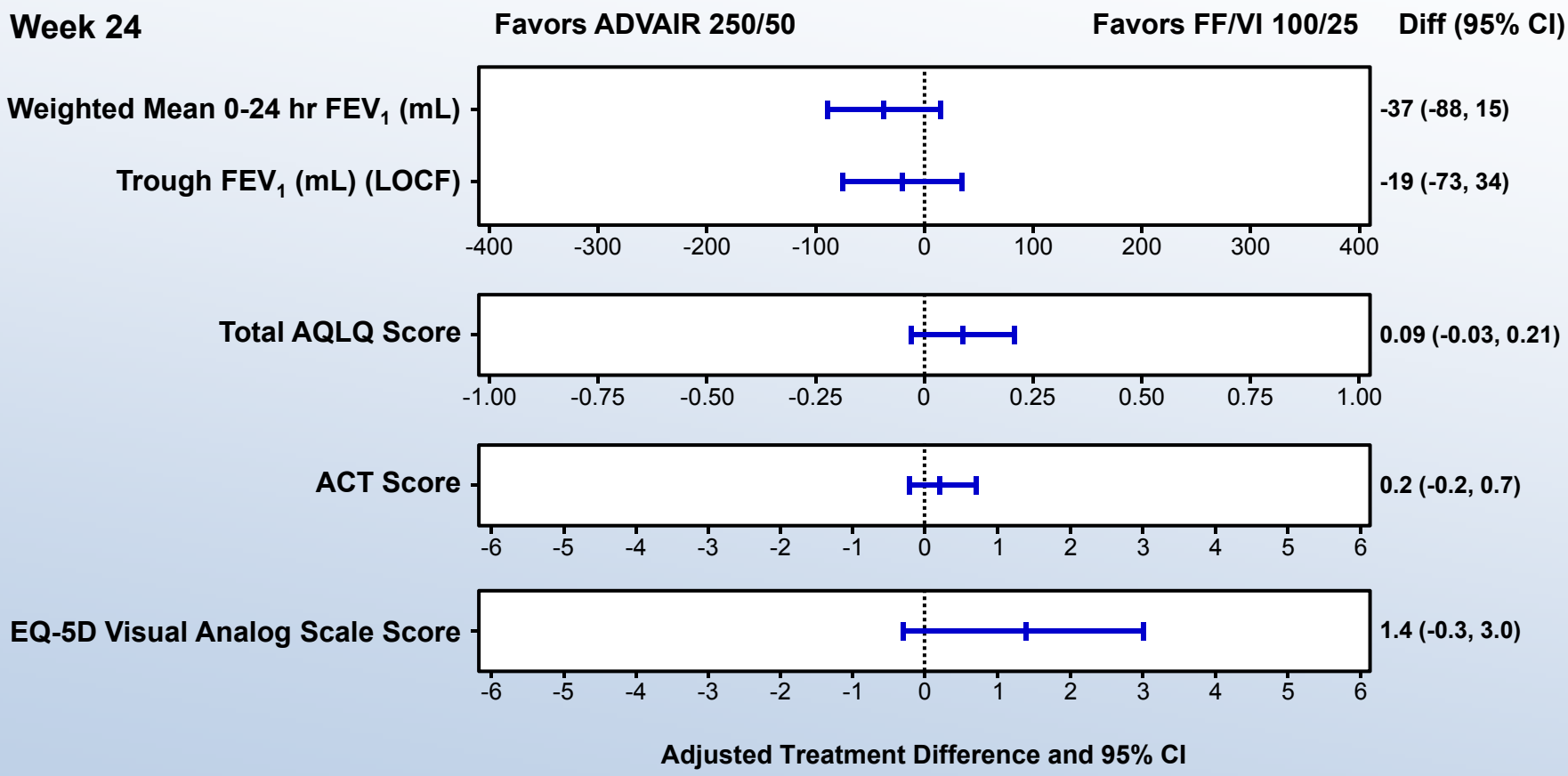
LABA step-up therapy was the most likely to provide the best response

Lemanske, et al. N Engl J Med 2010;362:975-85.

Efficacy of Fluticasone furoate / Vilanterol

- **Selection of Doses for Phase III**
  - Fluticasone furoate (FF)
  - Vilanterol (VI)
- **Phase III Program for FF/VI**
  - Efficacy of FF monotherapy: FEV_1 trough
  - Efficacy of FF/VI 100/25: FEV_1 trough and WM (0-24 hr)
  - Contribution of VI in the combination: FEV_1 trough and WM (0-24 hr)
  - Clinical benefit of FF/VI 200/25 over 100/25
- **Efficacy Data from Adolescent Sub-population**
- **Efficacy of FF/VI 100/25 QD vs. FP/SAL 250/50 BID**

Comparison of FF/VI 100/25 QD and ADVAIR 250/50 BID (Study 091)



Adapted from Woodcock et al, Chest 2013;144:1222-29.

Summary of Efficacy

- FF/VI provides sustained improvement in lung function
- Contribution of VI was demonstrated by the incremental improvement in lung function and symptoms
  - In one study, there was also a reduction in asthma exacerbations for FF/VI 100/25 compared with FF 100
- Efficacy of FF was demonstrated in the ARNUITY development program
- FF/VI 200/25 showed numerical improvements in lung function and symptoms compared with FF/VI 100/25
- No difference in treatment effects of FF/VI 100/25 QD and ADVAIR 250/50 BID

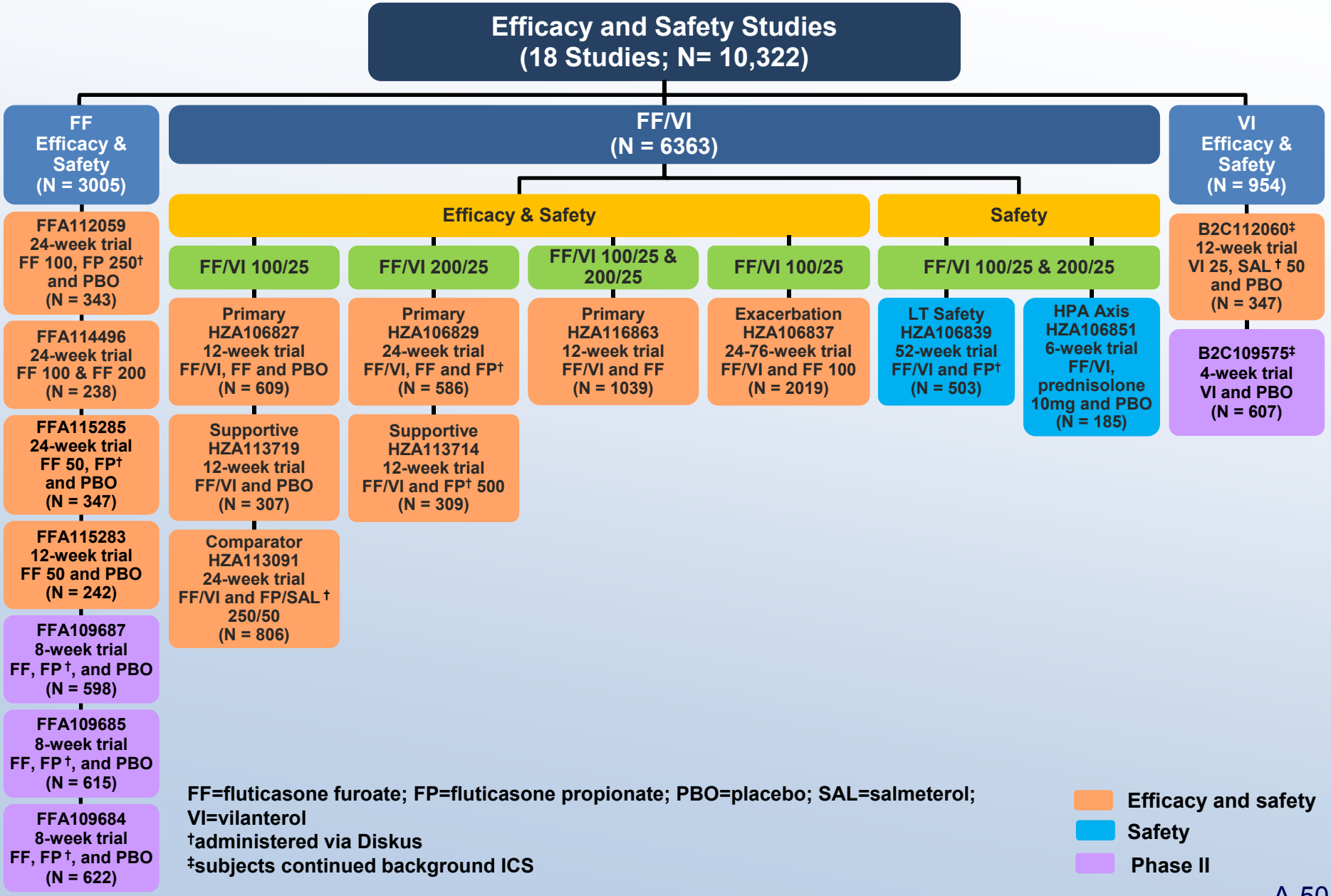
Conclusion

The breadth of data from our clinical development program demonstrates that FF/VI 100/25 is efficacious in the management of patients with asthma. Recognizing the need to titrate therapy to manage patients with different asthma severities, the data also supports the clinical utility of FF/VI 200/25.

Safety of Fluticasone furoate / Vilanterol

- Adverse and serious adverse events and deaths
- Adverse events of special interest
  - ICS
    - HPA and ocular effects
  - LABA
    - Cardiovascular effects
- Asthma composite endpoint
  - Hospitalization, intubation and death
- Overall benefit : risk

Integrated Studies for Safety



FF=fluticasone furoate; FP=fluticasone propionate; PBO=placebo; SAL=salmeterol; VI=vilanterol

†administered via Diskus

‡subjects continued background ICS

Efficacy and safety

Safety

Phase II

Common Adverse Events Integrated Data

Event, n (%)	Placebo N = 1070	FF/VI 100/25 N = 2369	FF/VI 200/25 N = 956	FF 100 N = 2010	FF 200 N = 608	VI 25 N = 216
Headache	74 (7)	322 (14)	85 (9)	260 (13)	44 (7)	17 (8)
Nasopharyngitis	59 (6)	277 (12)	76 (8)	207 (10)	53 (9)	9 (4)
Upper respiratory tract infection	30 (3)	155 (7)	52 (5)	123 (6)	15 (2)	4 (2)
Bronchitis	16 (1)	80 (3)	24 (3)	104 (5)	15 (2)	0
Oropharyngeal pain	13 (1)	72 (3)	27 (3)	75 (4)	19 (3)	7 (3)
Cough	13 (1)	86 (4)	18 (2)	74 (4)	13 (2)	0
Sinusitis	8 (<1)	70 (3)	16 (2)	55 (3)	15 (2)	0
Back pain	4 (<1)	66 (3)	22 (2)	59 (3)	11 (2)	2 (<1)
Influenza	9 (<1)	64 (3)	19 (2)	49 (2)	17 (3)	1 (<1)

Note: Table lists preferred terms of AEs seen in ≥3% in FF/VI 100/25 and FF/VI 200/25 groups

Exposure Adjusted Common Adverse Events Integrated Data

Event per Subject Year (SY)	Placebo SY = 214.9	FF/VI 100/25 SY = 1537.3	FF/VI 200/25 SY = 382.2	FF 100 SY = 1253.1	FF 200 SY = 169.2	VI 25 SY = 32.4
Headache	344.3	209.5	222.4	207.5	260.1	524.4
Nasopharyngitis	274.5	180.2	198.9	165.2	313.3	277.6
Upper respiratory tract infection	139.6	100.8	136.1	98.2	88.7	123.4
Bronchitis	74.4	52.0	62.8	83.0	88.7	0
Oropharyngeal pain	60.5	46.8	70.7	59.8	112.3	215.9
Cough	60.5	55.9	47.1	59.1	76.9	0
Sinusitis	37.2	45.5	41.9	43.9	88.7	0
Back pain	18.6	42.9	57.6	47.1	65.0	61.7
Influenza	41.9	41.6	49.7	39.1	100.5	30.8

SY=subject years

On-Treatment Serious Adverse Events in >1 Subject Integrated Data

Event, n (%)	Placebo N = 1070	FF/VI 100/25 N = 2369	FF/VI 200/25 N = 956	FF 100 N = 2010	FF 200 N=608	VI 25 N = 216
Any SAE	**7 (<1)**	**54 (2)**	**9 (<1)**	**41 (2)**	**7 (1)**	**1 (<1)**
Asthma exacerbation	1 (<1)	13 (<1)	1 (<1)	9 (<1)	1 (<1)	1 (<1)
Pneumonia	1 (<1)	4 (<1)	1 (<1)	6 (<1)	1 (<1)	0
Cholelithiasis	1 (<1)	1 (<1)	0	1 (<1)	0	0
Abscess	0	0	0	1 (<1)	1 (<1)	0
Atrial fibrillation	0	1 (<1)	1 (<1)	0	0	0
Breast cancer	0	1 (<1)	0	1 (<1)	0	0
Hypertension	0	1 (<1)	0	1 (<1)	0	0
Intervertebral disc protrusion	0	0	0	1 (<1)	1 (<1)	0
Limb traumatic amputation	0	0	1 (<1)	1 (<1)	0	0
Pyelonephritis	1 (<1)	0	0	1 (<1)	0	0
Subarachnoid hemorrhage	0	1 (<1)	0	1 (<1)	0	0

Fatal Events

- FF/VI 100/25
  - Car accident
- FF 100
  - Stage IV lung cancer (post-treatment)
  - Pneumonia
- Placebo (on a background of ICS)
  - Sudden death, cause unknown

Safety of Fluticasone furoate / Vilanterol

- Adverse events, serious adverse events and deaths
- **Adverse events of special interest**
  - ICS
    - HPA and ocular effects
  - LABA
    - Cardiovascular effects
- Asthma composite endpoint
  - Hospitalization, intubation and death
- Overall benefit : risk

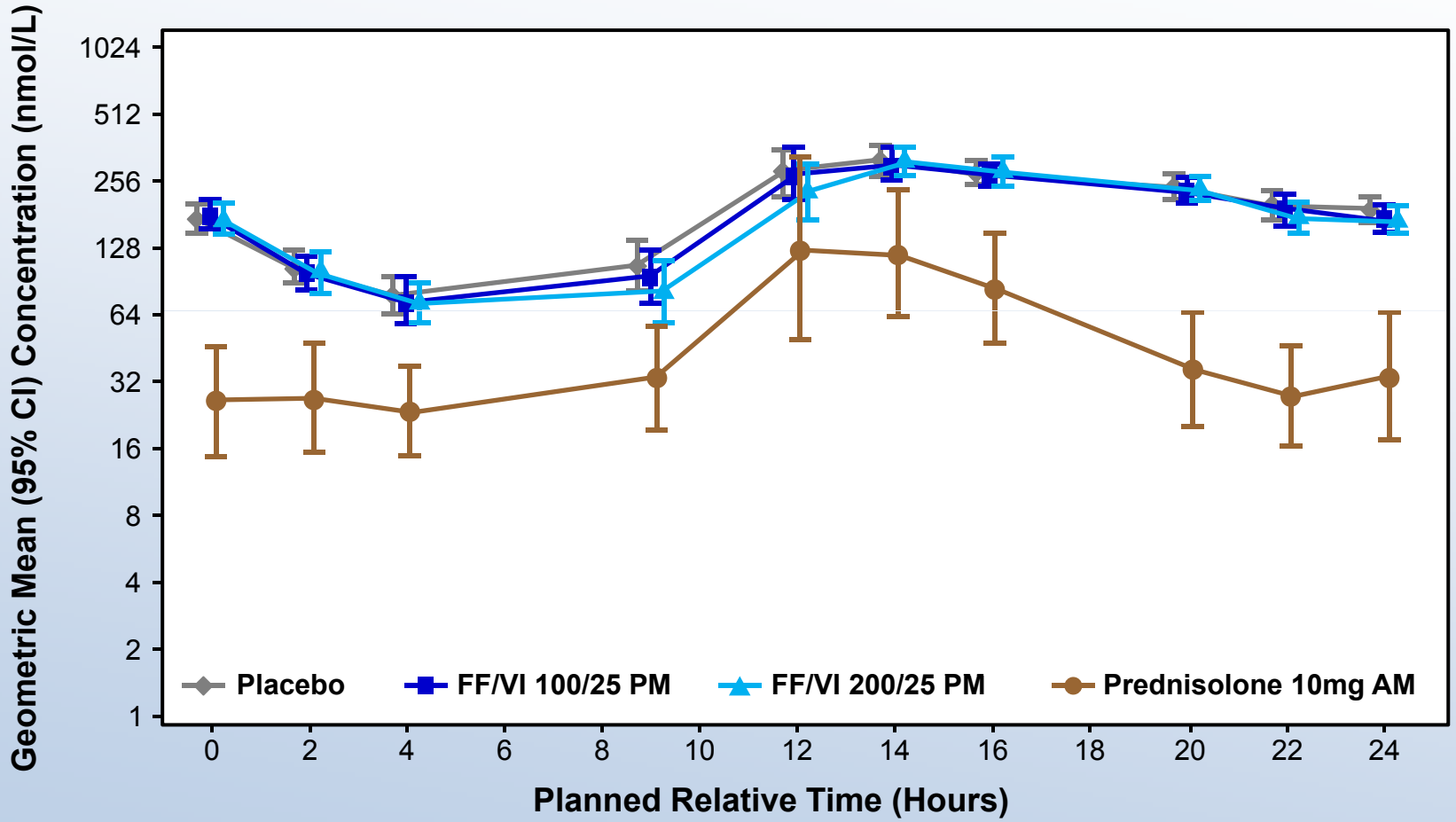
Other Tolerability: Adverse Events of Special Interest Integrated Data

Events, n (%)	Placebo N = 1070	FF/VI 100/25 N = 2369	FF/VI 200/25 N = 956	FF 100 N = 2010	FF 200 N=608
ICS-associated					
Systemic steroid effects	0	0	1 (<1)	0	0
Local steroid effects*	17 (2)	155 (7)	70 (7)	131 (7)	48 (8)
Effects on glucose†	0	10 (<1)	5 (<1)	12 (<1)	2 (<1)
Effects on bone	0	18 (<1)	3 (<1)	20 (<1)	2 (<1)
LABA-associated					
Tremor	0	1 (<1)	0	1 (<1)	2 (<1)
Hypertension	5 (<1)	45 (2)	6 (<1)	39 (2)	7 (1)
Effects on potassium	0	0	0	1 (<1)	0

*oropharyngeal pain, dysphonia, oral and oral pharyngeal candidiasis, throat irritation, candida infection, oral fungal infection, oropharyngitis, fungal

†Both ICS and LABA have potential effects on glucose

Geometric Mean Serum Cortisol Concentration (Study 851)



Allen et al. Clin Respir J 2013;7:397-406.

Ocular-associated Adverse Events of Special Interest Integrated Data

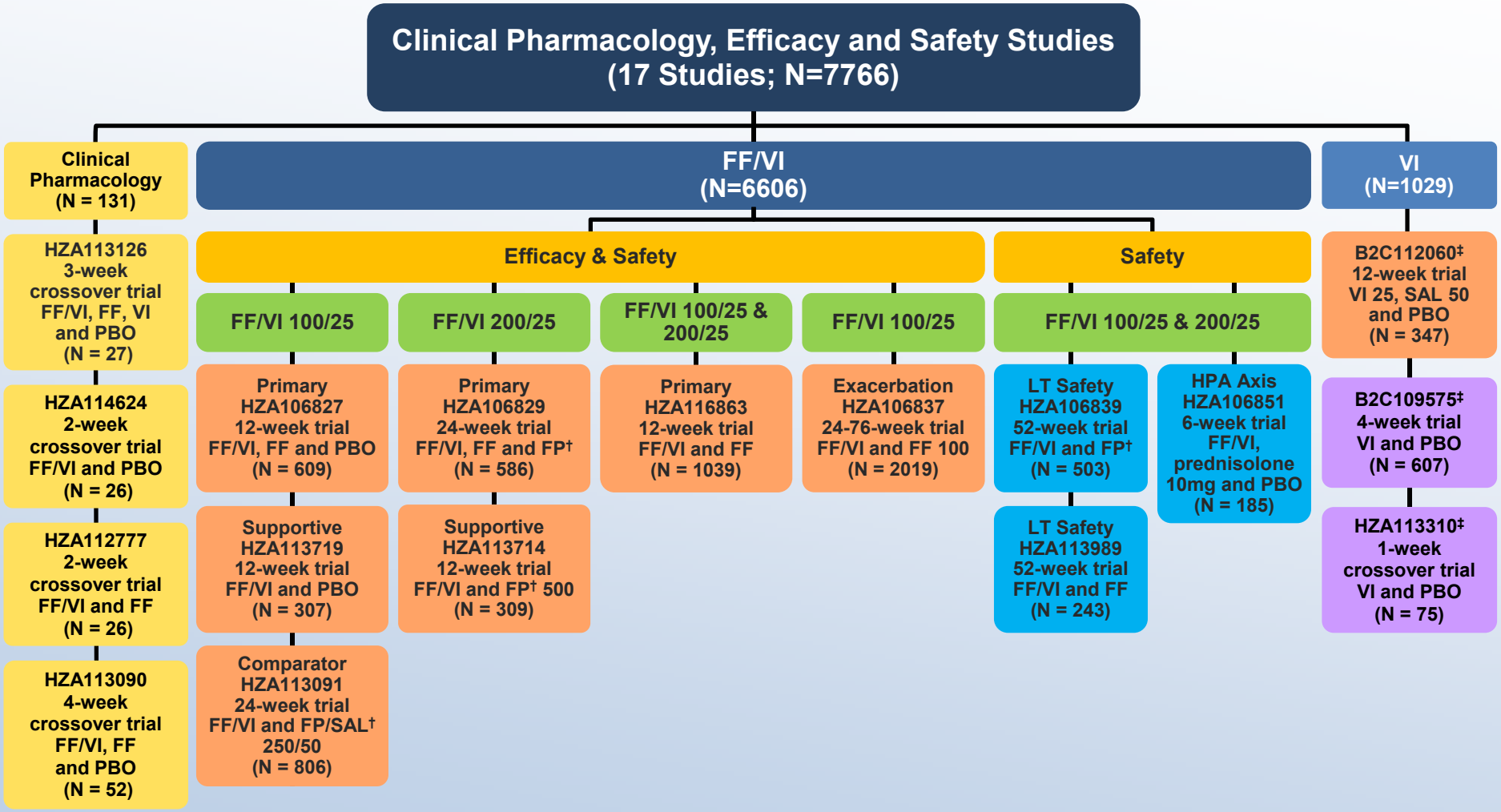
Events, n (%)	Placebo N = 1070	FF/VI 100/25 N = 2369	FF/VI 200/25 N = 956	FF 100 N = 2010	FF 200 N = 608	VI 25 N = 216
Any event	0	3 (<1)	2 (<1)	6 (<1)	0	0
Eye pain	0	2 (<1)	0	4 (<1)	0	0
Cataract	0	1 (<1)	1 (<1)	2 (<1)	0	0
Cataract cortical	0	0	1 (<1)	0	0	0

- Evaluation of Lens Opacification Classification System (LOCS III) in the year long safety study (Study 839) did not show any appreciable effects in cataracts or other lens opacities

Pre-Defined Arrhythmias of Potential Clinical Importance 24-hour Holter Monitoring (Study 839)

Arrhythmia, n (%)	FF/VI 100/25 N =201	FF/VI 200/25 N=202	FP 500 BID N=100
Number of subjects with Holter	111	115	50
Ventricular arrhythmias	2 (2)	3 (3)	0
Non sustained VT	2 (2)	2 (2)	0
Idioventricular rhythm	0	1 (<1)	0
Supraventricular arrhythmias	0	4 (3)	0
Sustained supraventricular tachycardia	0	3 (3)	0
Atrial fibrillation (rate >100 bpm)	0	1 (<1)	0
Junctional tachycardia	1 (<1)	0	0
Sinus pause (≥2 sec)	3 (3)	0	1 (2)
Abnormalities of repolarization	1 (<1)	1 (<1)	0
ST elevation	1 (<1)	0	0
ST depression	1 (<1)	1 (<1)	0

Studies in the Asthma Composite Assessment

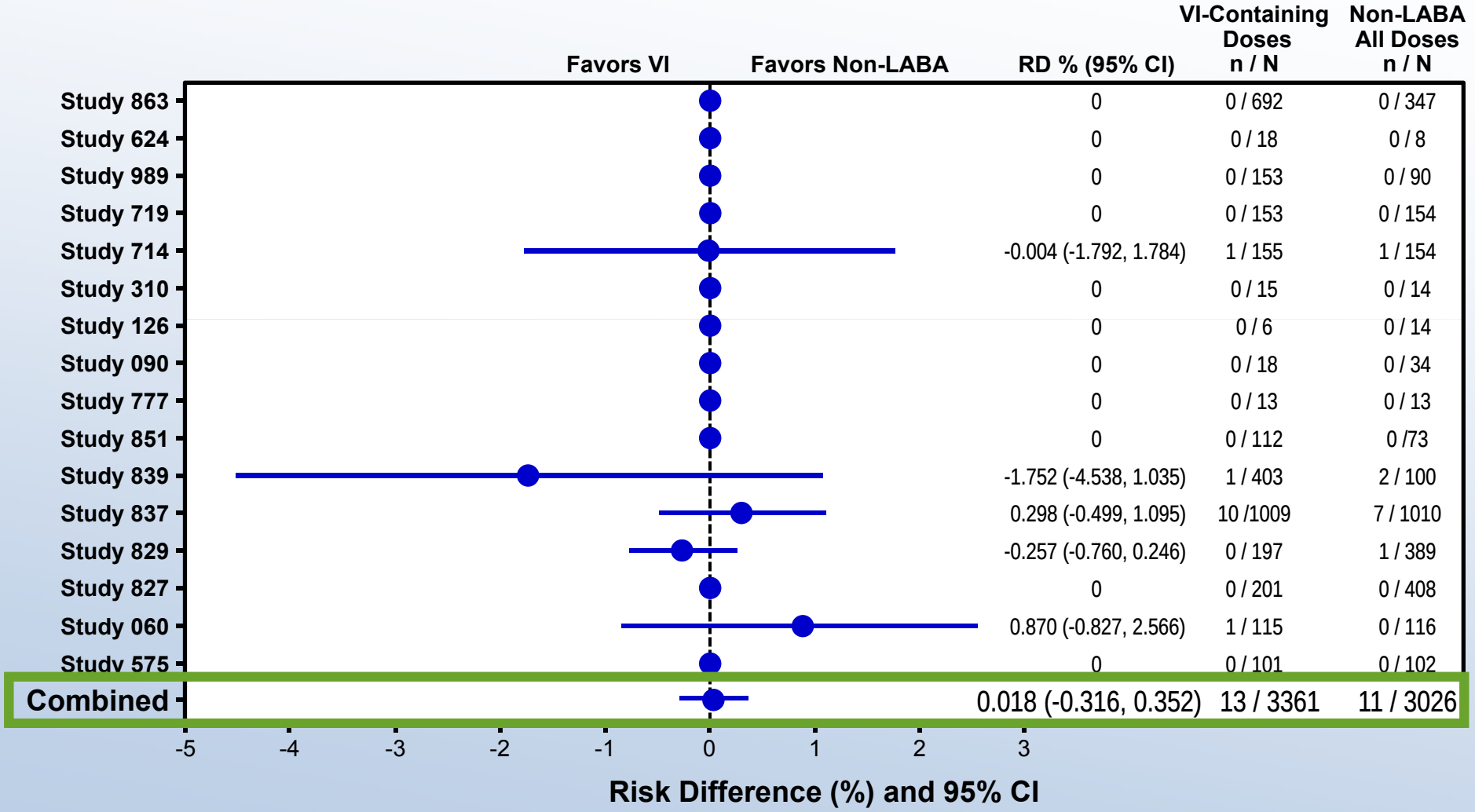


FF=fluticasone furoate; FP=fluticasone propionate; PBO=placebo; SAL=salmeterol; VI=vilanterol
†administered via Diskus
‡subjects continued background ICS

Asthma Composite Endpoint Adjudication

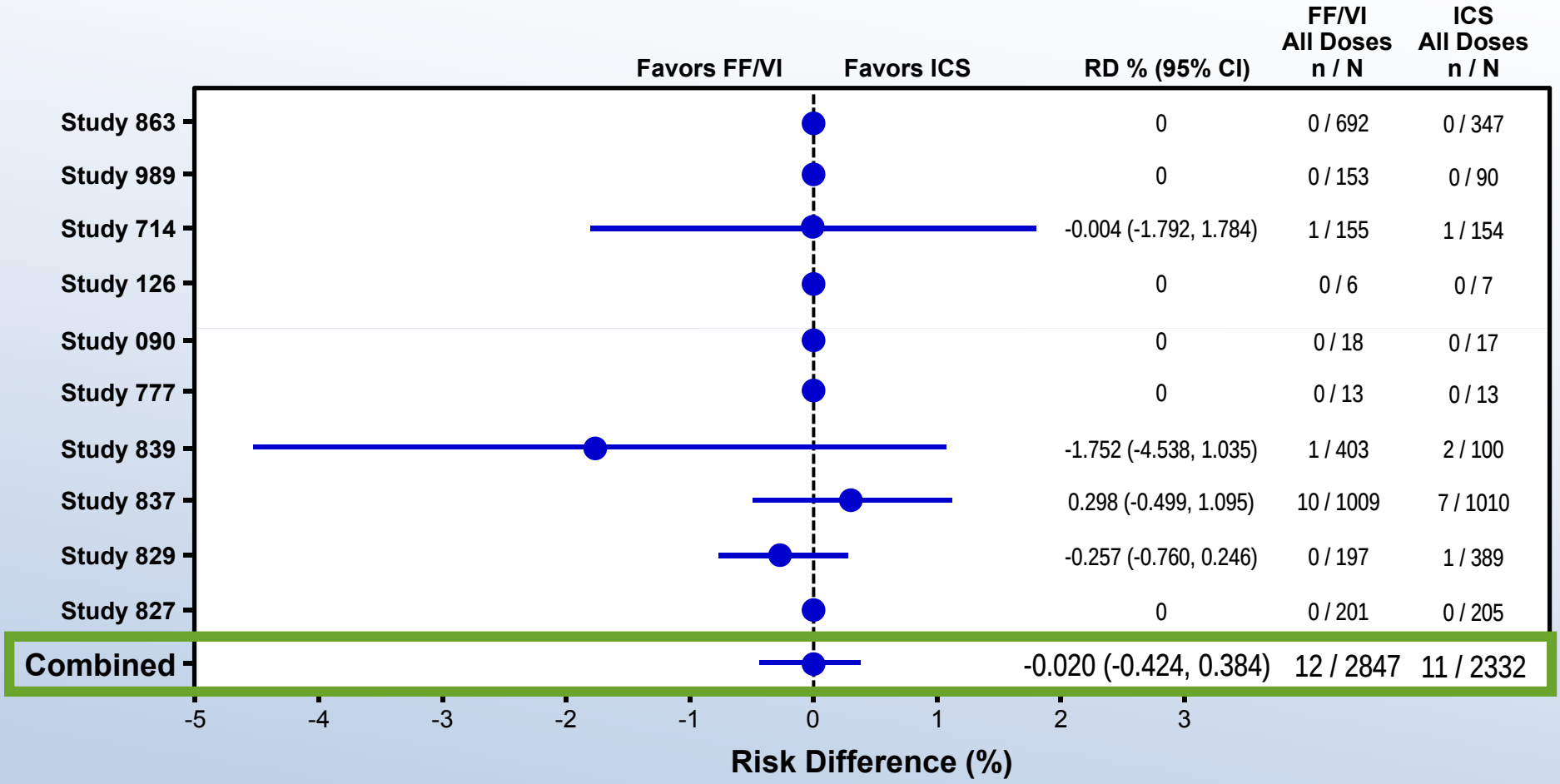
- A committee of three independent, experienced respiratory clinicians
- All SAEs were adjudicated in a blinded fashion to determine if they resulted in a hospitalization, intubation or death
- Each SAE determined to be a hospitalization, intubation or death was assessed:
  - Respiratory-related or not
  - If respiratory-related: asthma, COPD, pneumonia or another cause

Asthma Composite Endpoint
All VI-Containing Doses vs. All Non-LABA Doses



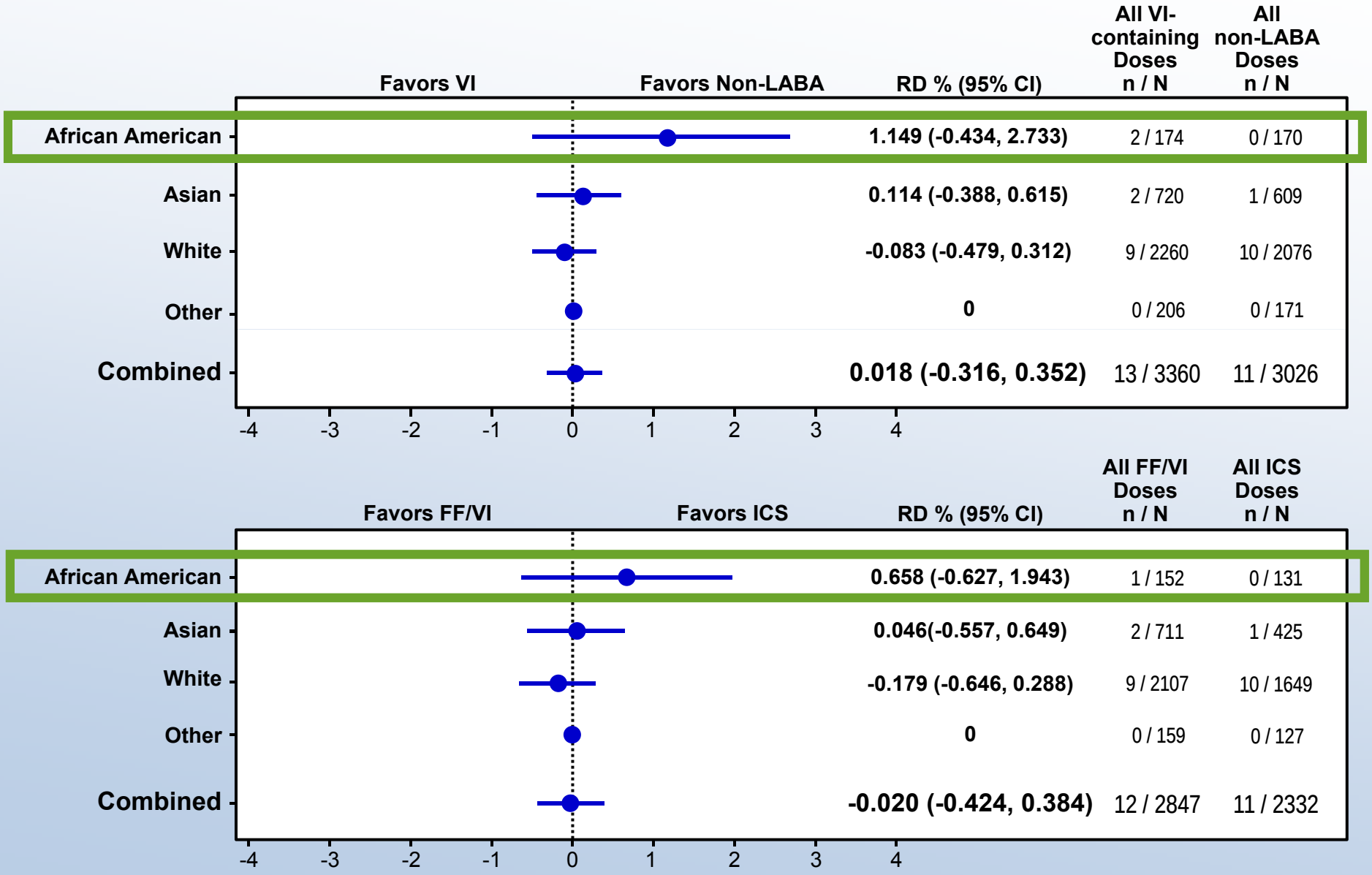
- **No asthma-related deaths or intubations**

Asthma Composite Endpoint
All FF/VI Doses vs. All ICS Doses

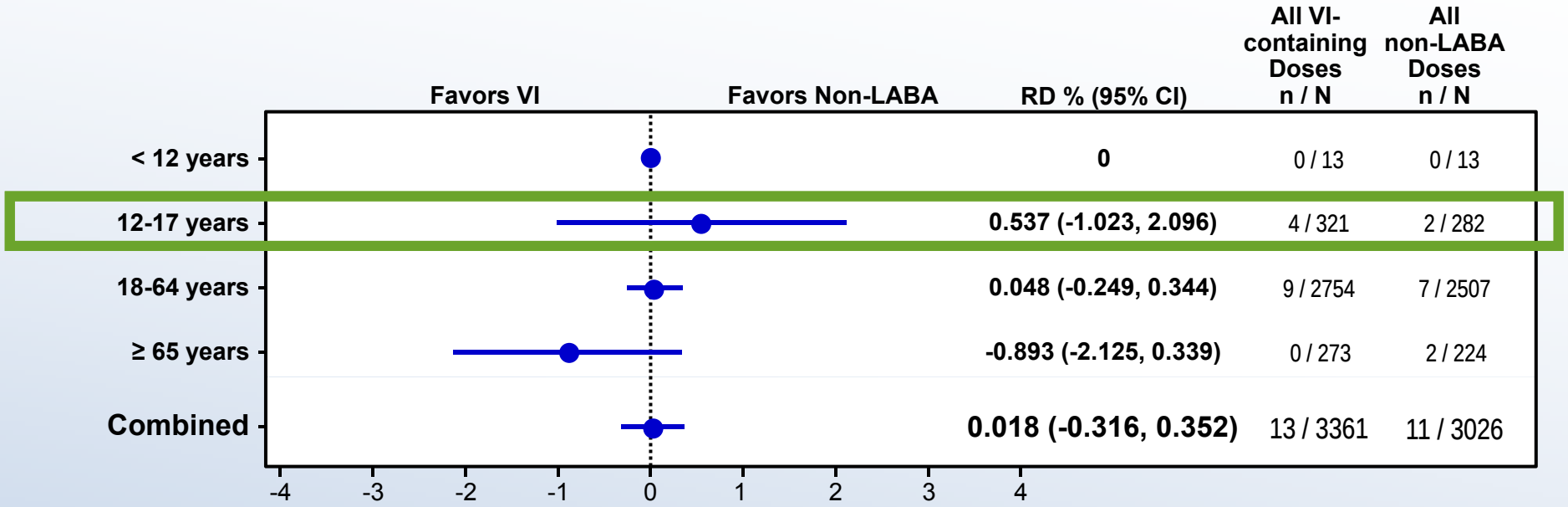


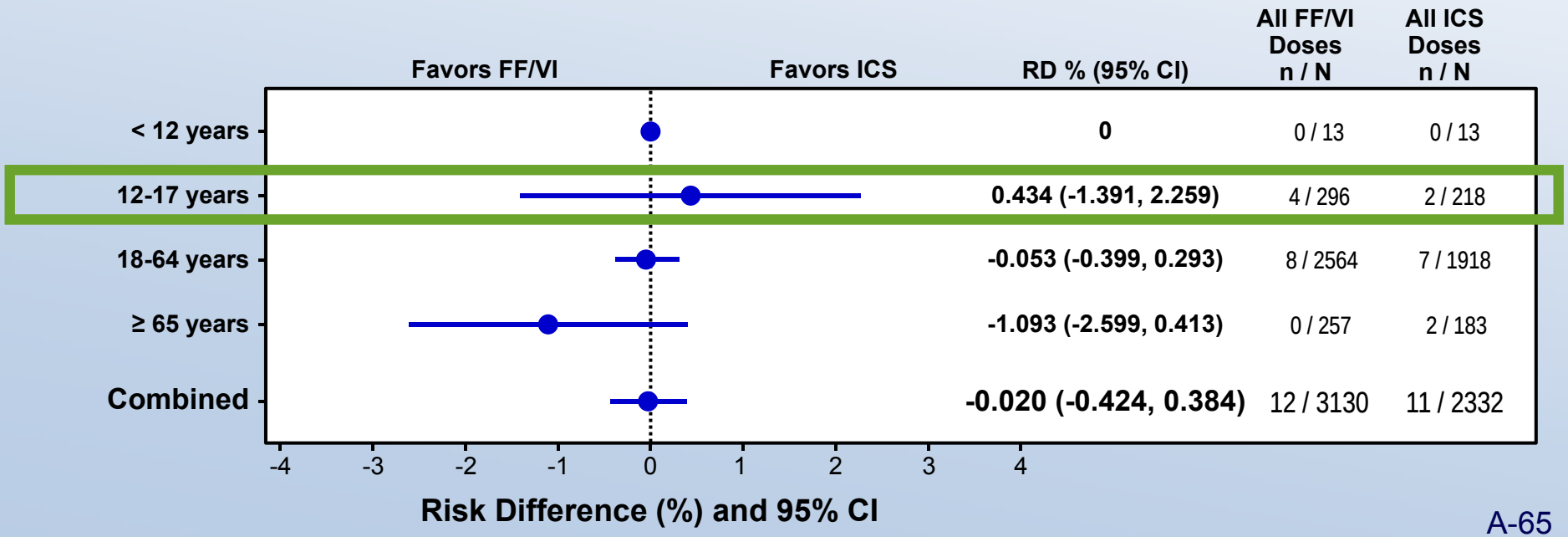
- No asthma-related deaths or intubations
- 23 asthma-related hospitalizations: 12 with FF/VI and 11 with ICS

Asthma Composite Endpoint by Race



Asthma Composite Endpoint by Age

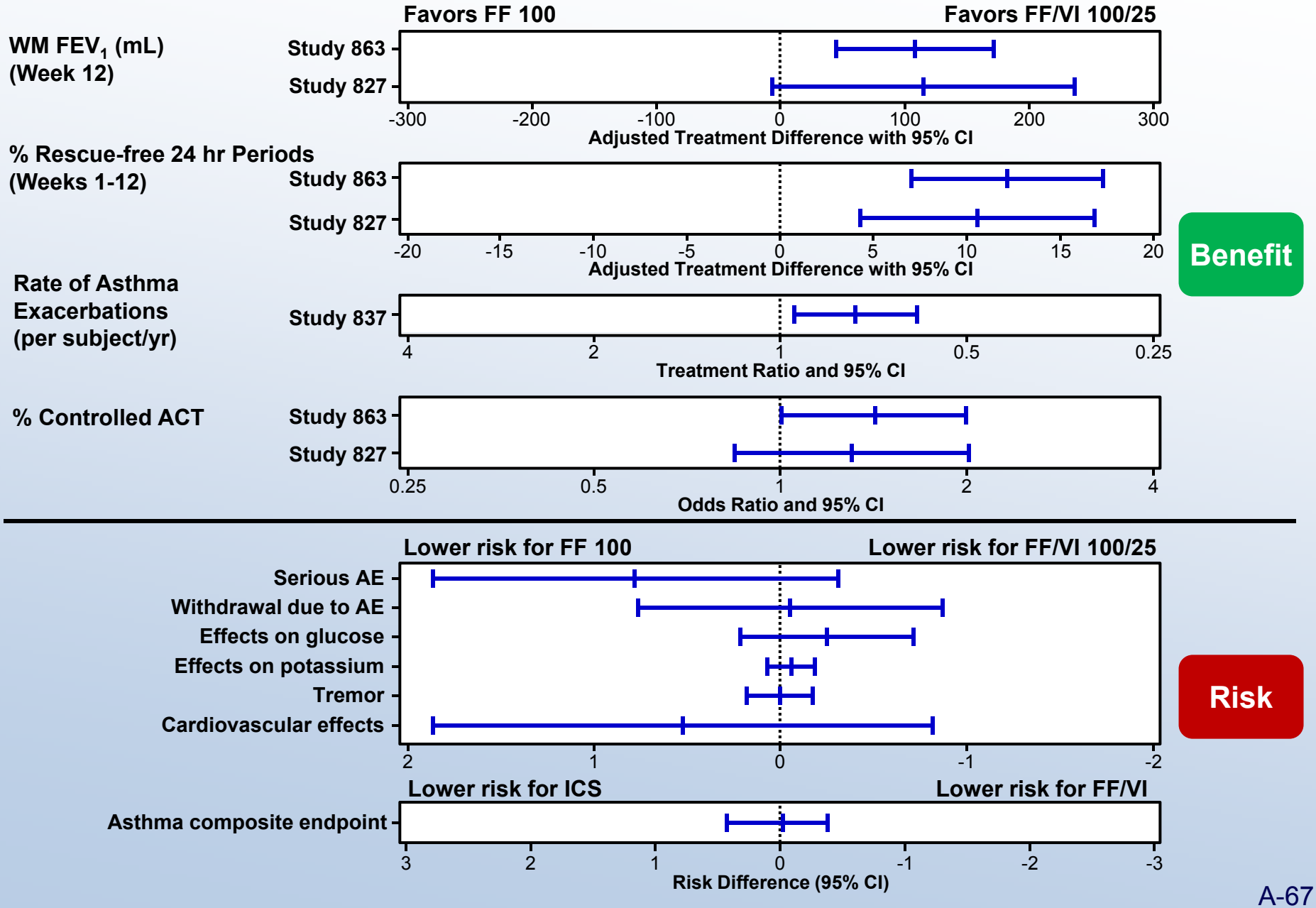




Safety Summary

- AE and SAE profile consistent with classes
- Adverse events of special interest
  - No HPA-axis suppression
  - Minimal ocular effects of FF/VI
  - No clinically relevant differences for cardiovascular events
- No increase in asthma composite endpoint in VI-containing treatment arms

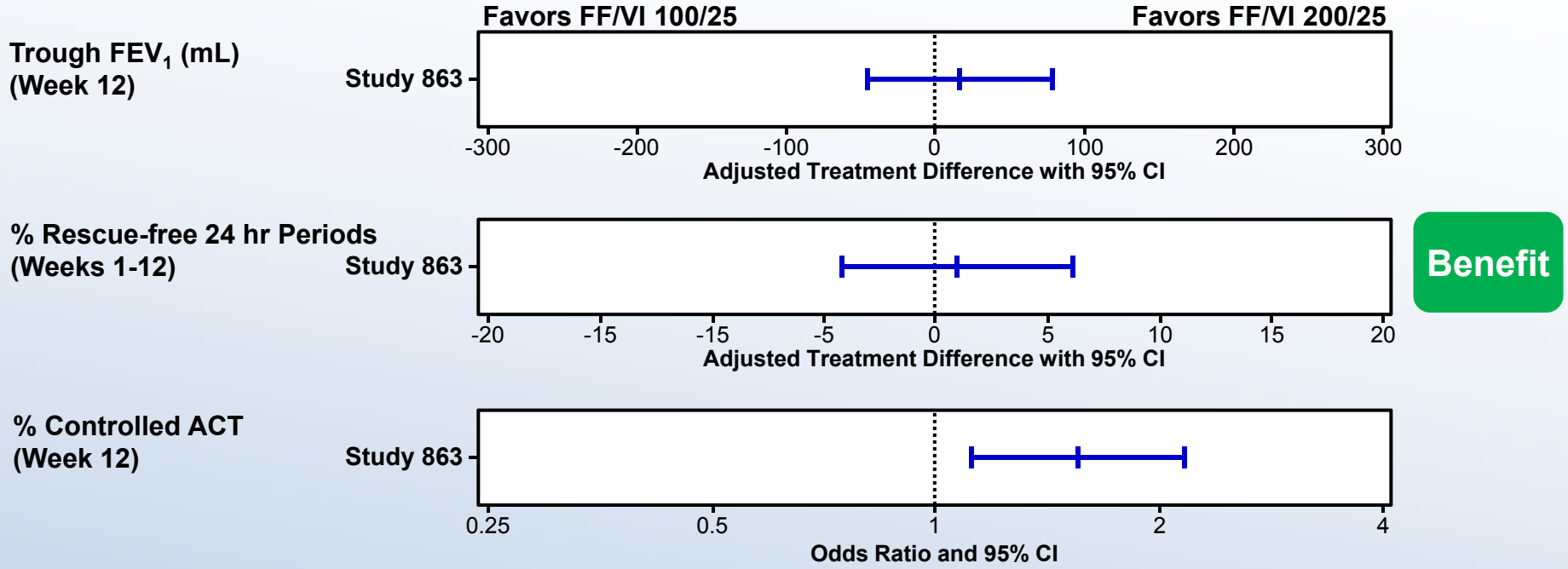
Benefit : Risk FF/VI vs. FF



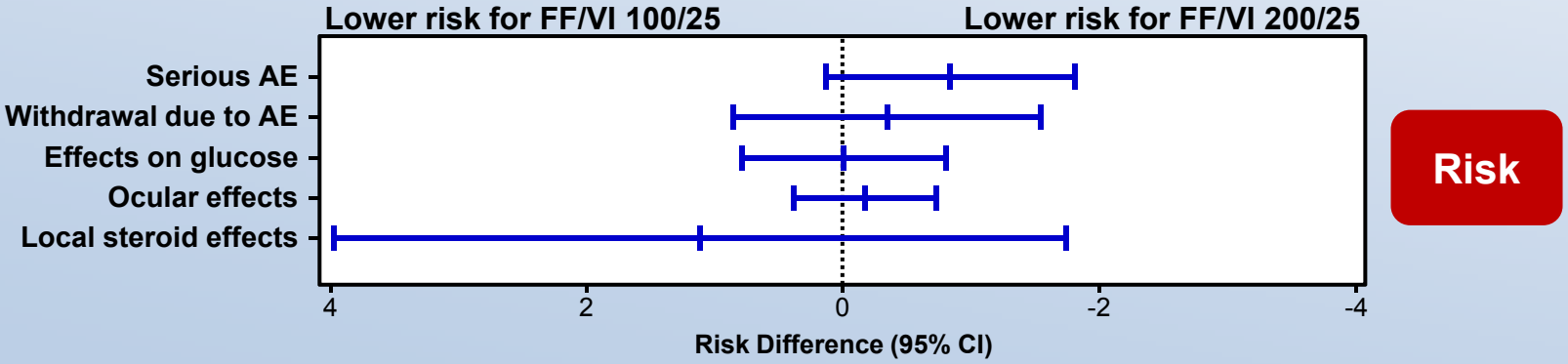
Benefit : Risk FF/VI vs. FF in Adolescents

- The program was not designed to statistically demonstrate the benefit of FF/VI over FF in the adolescent subgroup
- The effect on lung function favored FF/VI over FF in pooled analysis at week 12
  - Variable lung function response in the pivotal studies that only included 6% or less adolescents
- In the 837 exacerbation study
  - 93mL treatment difference favoring FF/VI over FF in trough FEV_1 at week 12
  - Although no difference in exacerbations was observed, the exacerbation rate was 100 times less than the adult population
- For the asthma composite endpoint, there were four hospitalization events in the FF/VI arm and two in the ICS-containing arm and the confidence interval crossed zero with the upper bound risk difference just over 2%

Benefit : Risk of 200/25 vs. 100/25



Benefit



Risk

Clinical Perspectives on Asthma Management

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Disclosures
Eugene R. Bleecker, MD

Listed are all of my relationships that *may* be related to this presentation that have existed during the past 3 years:

- **Industry-sponsored Clinical Trials (Through Wake Forest Health Sciences):** Amgen, AstraZeneca-MedImmune, Boehringer-Ingelheim-Pfizer, Cephalon-TEVA, Forest, Genentech-Roche, GlaxoSmithKline, Janssen-Johnson and Johnson, Novartis, Pearl, Pfizer, Sanofi-Aventis-Regeneron

- **Consultancy:** AstraZeneca, Boehringer-Ingelheim-Pfizer, Janssen-Johnson & Johnson, Genentech-Novartis, GlaxoSmithKline, Merck, Sanofi-Adventis/Regeneron

- **NIH Grants (NHLBI):** ***Severe Asthma Research Program (SARP); AsthmaNet; Spiromics; Pharmacogenetics of Asthma***; Linking Genetics, Genomics and Phenomics to Better Understand Asthma Severity; CAPPA Consortium

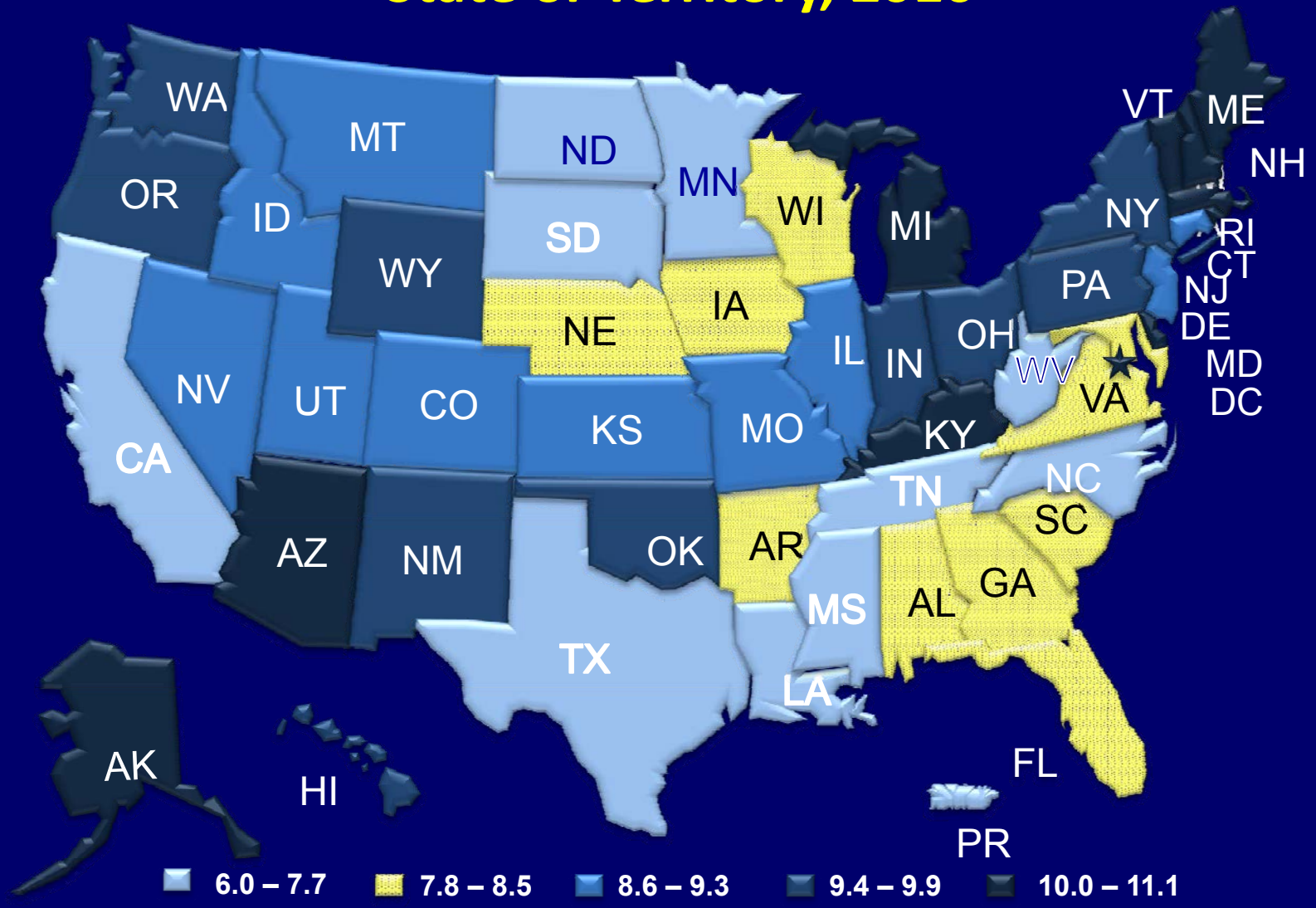
- **No personal relationships with tobacco industry entities.**
- **No Off-Label Disclosure.**

Asthma is a Serious Disease with Major Public Health Impact

- 18.7 million adults (8.0%) and 6.8 million children (9.3%) have asthma
- Asthma accounts yearly for:
  - 15.5 million outpatient visits
  - 1.8 million emergency department visits
  - 439,000 hospitalizations (3.6 day average stay)
- 3630 patients died from asthma in 2013
- Asthma is often poorly controlled despite available treatments (49% of adults and 58% of children have ≥1 asthma attacks)

2013 National Health Interview Survey (NHIS) Data. Available at: http://www.cdc.gov/asthma/nhis/2013/data.htm
Moorman et al. National Surveillance of Asthma: United States, 2001–2010, Vital Health Stat 2012;3(35):27

Adult Self-Reported Current Asthma Prevalence (%) by State or Territory, 2010



CDC, BRFSS, 2010. Available at http://www.cdc.gov/asthma/asthmadata.htm, Accessed 17Feb2015.

The Challenge

Clinical asthma is characterized by phenotypic variation

How do we effectively manage asthma heterogeneity and differing levels of disease severity?

Important Clinical Management Issues in Asthma

- Individualized controller and preventive options in asthma
- Improved adherence and better therapeutic efficacy
- Safe and effective asthma therapies for our patients

Asthma Control Assessment

Impairment

- Symptoms
- Nighttime awakenings
- SABA use for symptom control
- FEV_1 or peak flow
- Interference with normal activity
- Validated questionnaires
  - ATAQ
  - ACQ
  - ACT

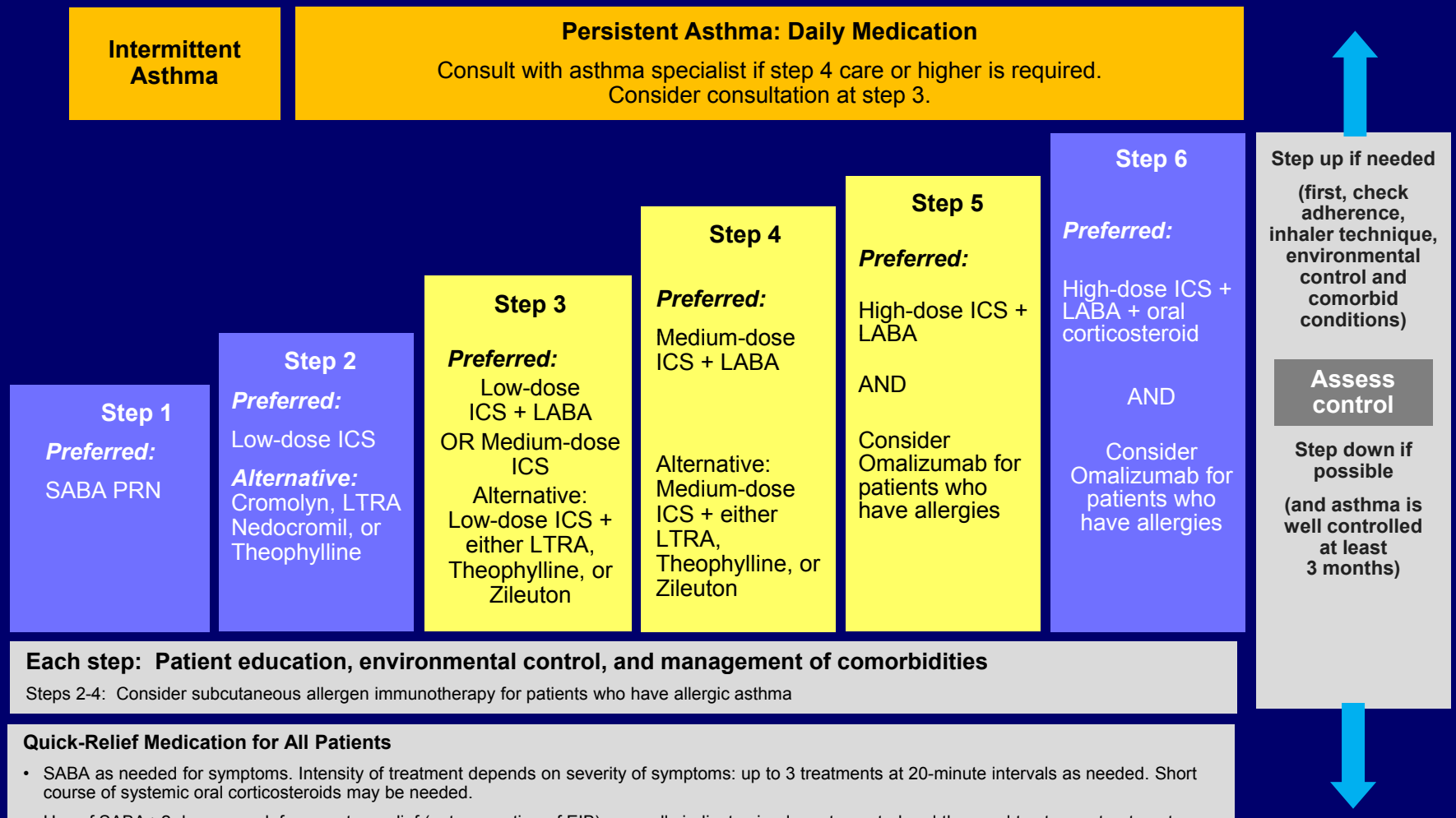
Risk

- Exacerbations
- Progressive loss of lung function
- Treatment-related adverse events

Adapted from *Guidelines for the Diagnosis and Management of Asthma (EPR-3) 2007*. NIH, NHLBI. August 2007. NIH publication no. 08-4051.

NIH / NAEPP Asthma Guidelines

Stepwise Approach for Managing Asthma (≥12 Years)



Each step: Patient education, environmental control, and management of comorbidities

Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma

Quick-Relief Medication for All Patients

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of systemic oral corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

Key: ICS, inhaled corticosteroid; LABA, inhaled long-acting beta$_2$-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

***Guidelines for the Diagnosis and Management of Asthma (EPR-3) 2007*. NIH, NHLBI. August 2007. NIH publication no. 08-4051.**

Treating the Spectrum of Asthma

Severe Asthma Definition: Asthma which requires treatment with guidelines suggested medications: high dose ICS and LABA for the previous year or systemic CS to prevent it from becoming "uncontrolled" or asthma remains "uncontrolled" despite this therapy

Prevalence of severe asthma is estimated as 5-10% of total asthma population

ATS ERS Task Force On Severe Asthma Chung et al. Eur Respir J 2014;43:343–73

Clinical Heterogeneity in Asthma

- Limitations of Guidelines Asthma Classification
  - Does not adequately reflect heterogeneity within and across asthma severity levels
  - Assumes all patients within a severity level respond to the same therapies
- Because of asthma heterogeneity, multiple controller therapies (e.g. ICS, ICS/LABA, etc.) with flexible dosing are required to achieve optimal management in asthma

Moore et al. Am J Respir Crit Care Med 2010;181:315-323.
Jarjour, et al. Am J Respir Crit Care Med 2012;185:356-62.

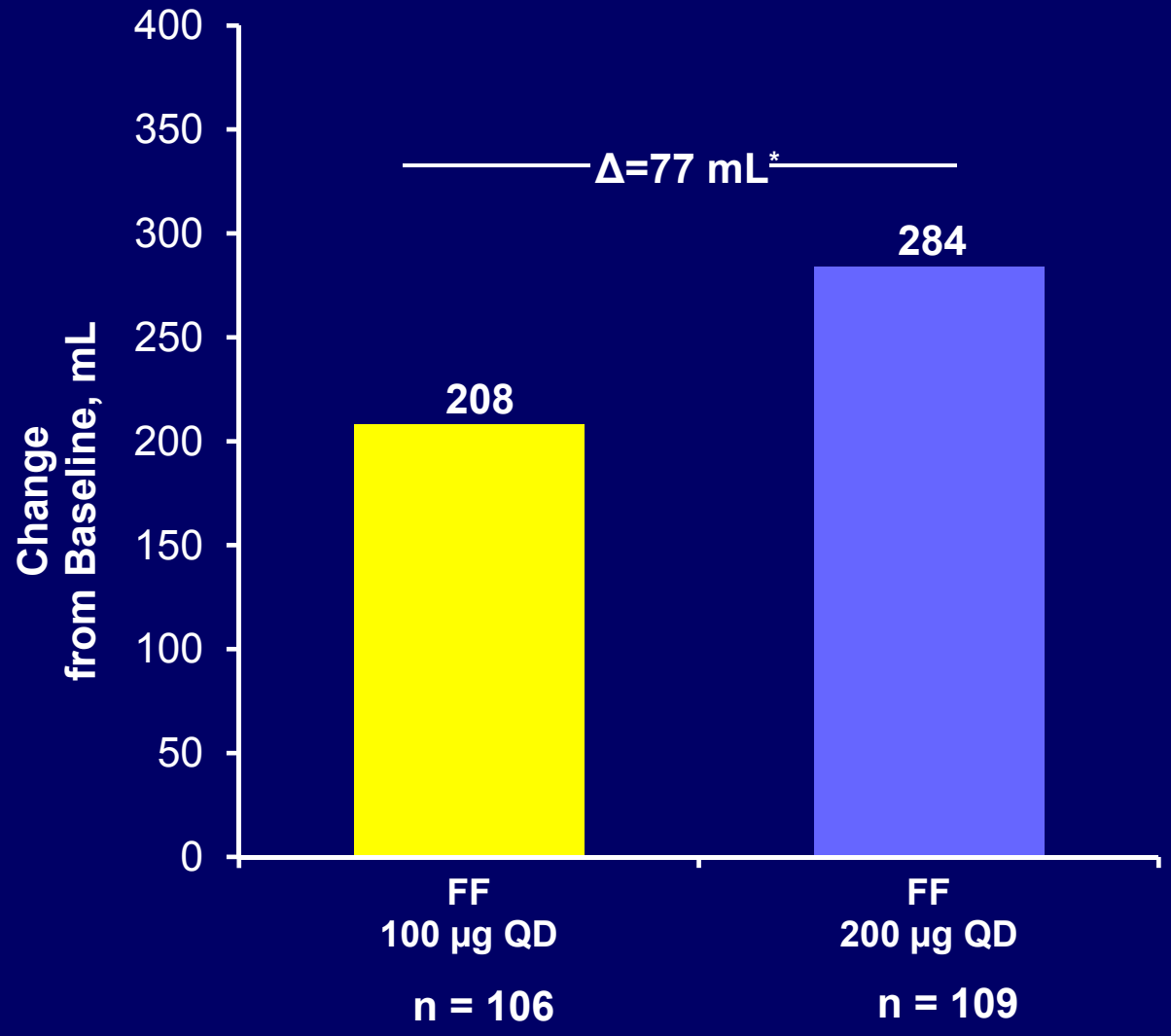
Asthma Management: *Issues*

- **Specific Treatment Issues**
  - Adolescent asthma
  - Dosing flexibility
  - Consistent inhaler availability
  - Adherence

Asthma Management: *Issues*

- **Specific Treatment Issues**
  - Adolescent asthma
  - Dosing flexibility
  - Consistent inhaler availability
  - Adherence

Improvement in FEV_1 with Increasing Doses of Fluticasone Furoate (FF)



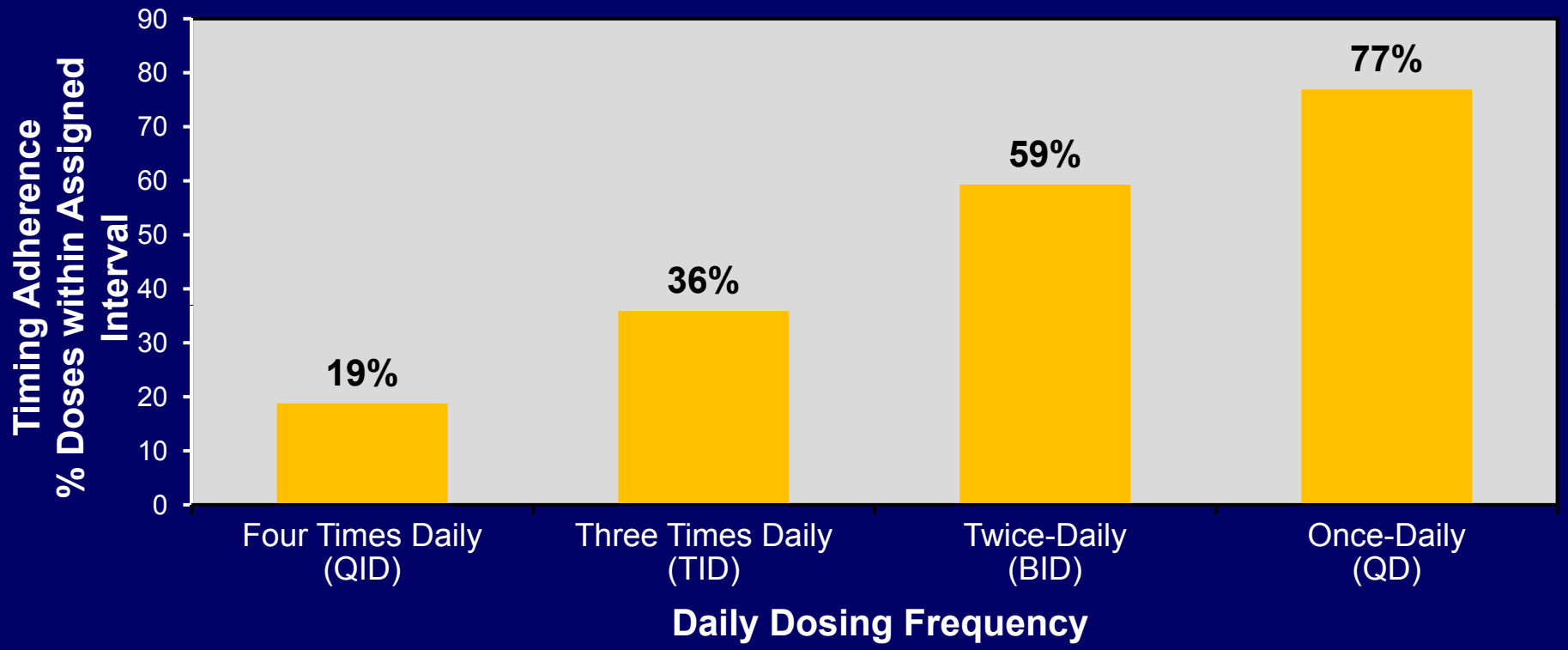
*95% CI: -39,192; this was a descriptive trial therefore no p-value is available for this comparison.

Woodcock, et al. BMC Pulmonary Medicine. 2014;14(1)

Too many inhalers are confusing to most asthmatics and health providers:

Combination inhalers with dosing flexibility are very important

Dosing Frequency and Adherence



- In chronic diseases, less frequent dosing is associated with improved adherence

Coleman, et al. J Manag Care Pharm. 2012;18:527-39.

Personalized Asthma Management

- Asthma is a heterogeneous disease characterized by different severity phenotypes

Thus, appropriate asthma management requires effective and safe pharmacologic approaches that facilitate individualized therapeutic strategies

BREO ELLIPTA Benefits in Asthma Management

- Improves lung function
- Decreases symptoms, SABA use and improves asthma control
- Decreases asthma exacerbations vs. ICS alone
- Similar safety profile to current ICS/LABA products
- Provides the ability to address asthma heterogeneity and provides titration of therapy with the same inhaler
- Once-daily therapy should improve adherence

Bleecker, et al. J Allergy Clin Immunol Pract 2014;2:583-61.
Bateman et al. Thorax 2013;4:312-19.
O'Byrne, et al. Eur Respir J 2014;43:773-82.

Closing Remarks

Katharine Knobil, MD

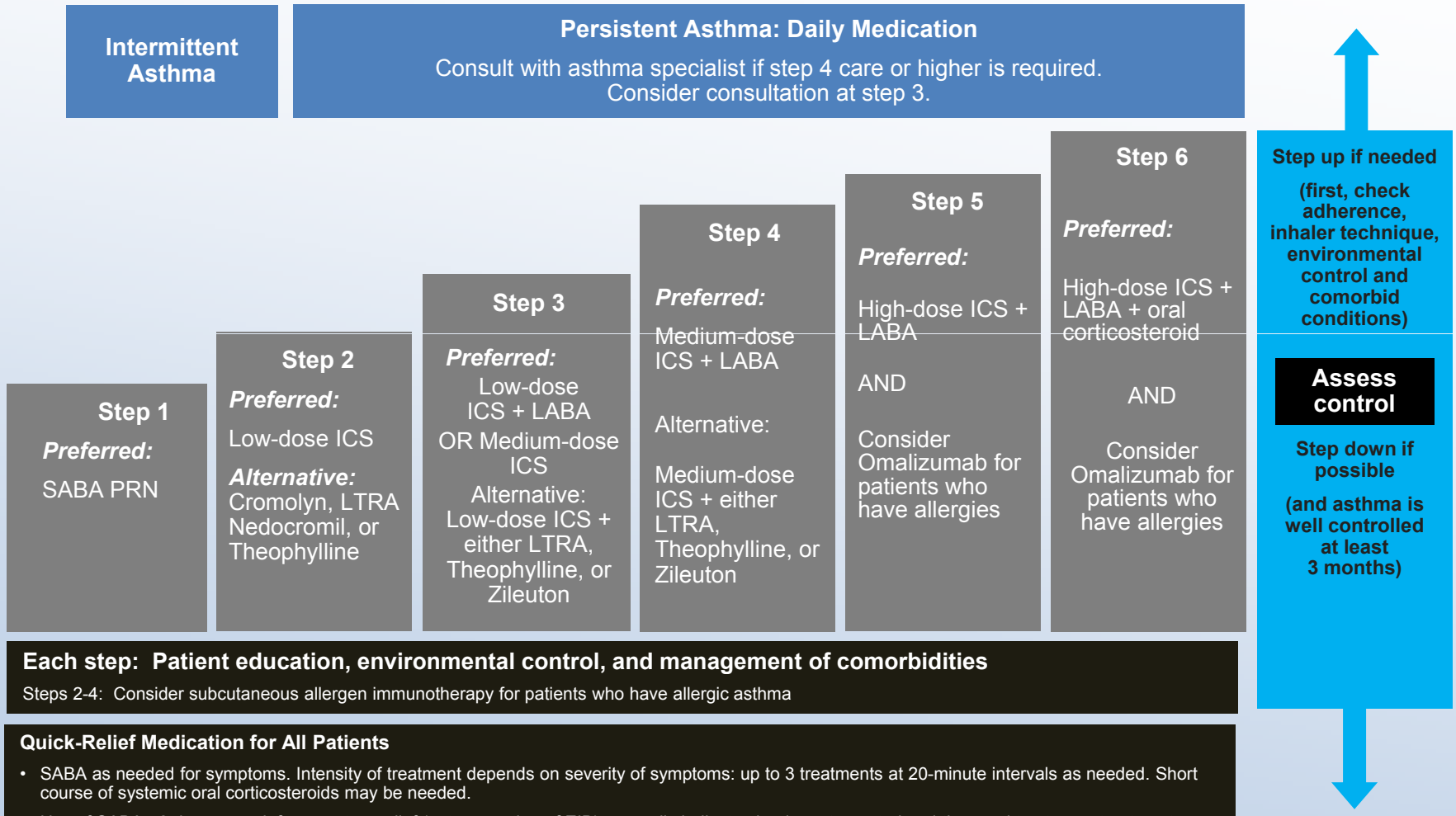
Summary of the BREO ELLIPTA Asthma Development Program

- New, once daily treatment option for patients with asthma
- Robust clinical programs in asthma and COPD (N >20,000)
- Established class of medications for the treatment of asthma
  - ICS component approved for asthma (FF)
- Efficacy
  - 24 hour improvement in lung function with BREO ELLIPTA
  - Improvements in symptoms of asthma
  - 20% relative reduction in the risk of experiencing an asthma exacerbation
- Safety
  - Extensive safety database
  - Safety profile similar to established ICS/LABA combinations
  - No increase in serious asthma-related outcomes

Extensive Data Show No Increased Risk in Serious Asthma Outcomes with LABAs when used with ICS

- ADVAIR: 22,000 patients
  - No asthma-related deaths or intubations
  - No increased risk of hospitalizations
- BREO program: 7,766 patients included in asthma composite endpoint
  - No asthma-related deaths or intubations
  - No increased risk of hospitalizations
- Ongoing LABA safety studies: over 17,000 patients randomized
  - No asthma-related deaths
  - 2 asthma-related intubations in adult and adolescent study
- Another study for BREO to evaluate hospitalizations would be unlikely to meaningfully add to currently available evidence and ongoing studies

Stepwise Approach for Managing Asthma in Youths ≥12 Years of Age and Adults



Key: ICS, inhaled corticosteroid; LABA, inhaled long-acting beta$_2$-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

***Guidelines for the Diagnosis and Management of Asthma (EPR-3) 2007*. NIH, NHLBI. August 2007. NIH publication no. 08-4051.**

BREO ELLIPTA for Asthma

- *BREO ELLIPTA is a combination ICS/LABA indicated for the once-daily treatment of asthma in patients aged 12 years and older.*
- *The recommended starting dosage of BREO ELLIPTA is 100/25 or BREO ELLIPTA 200/25 administered as 1 inhalation once daily.*

BACKUP SLIDES

Table 48: Total Subjects Treated in the FF/VI Asthma Clinical Program (ITT)

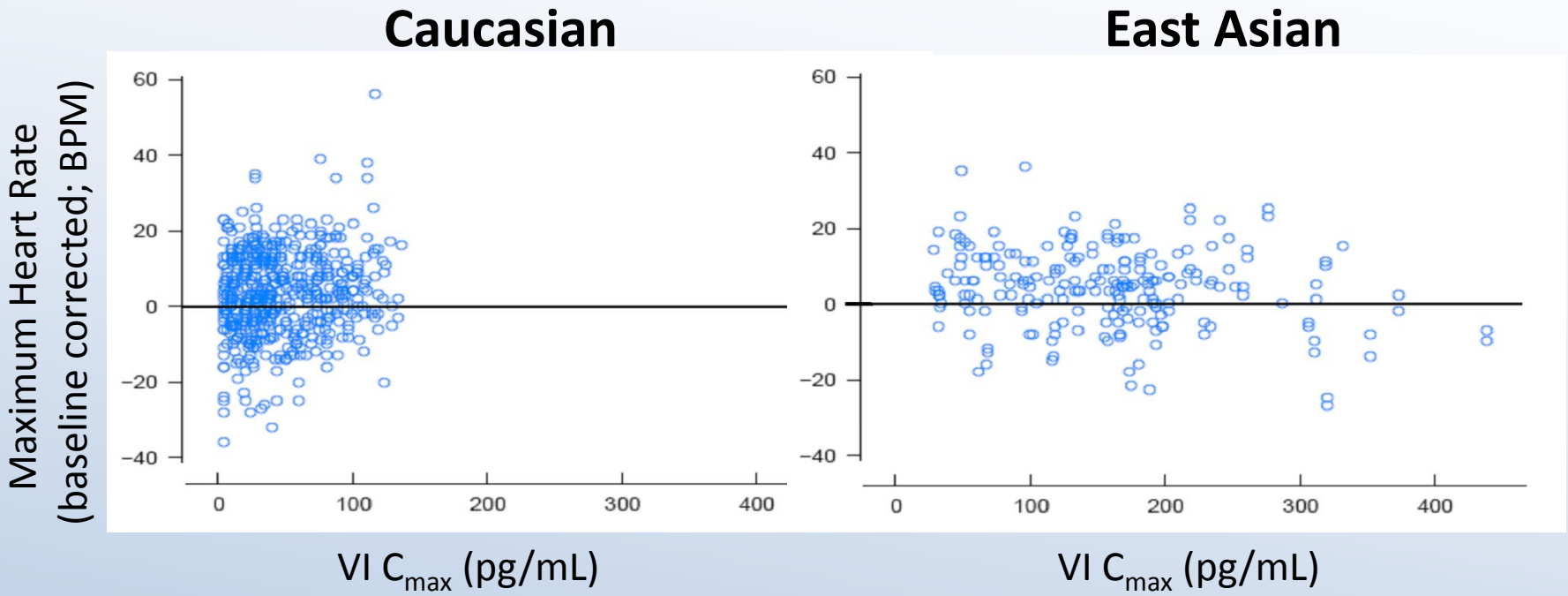
Study Grouping	Total Subjects Treated[1]			
	ITT[2]	FF/VI[3]	FF[3]	VI[3]
Integrated Studies[4]	10,322[5]	3325	3565	620
Non-integrated Studies[4, 6]	1729	153	1162	61
Clinical Pharmacology	1328	397	747	395
Adult (18-75 years)	1247	372	696	368[7]
Pediatric (5-11 years)	81	25	51	27
Program Total	13,379	3875	5474	1076

Source: Table 1.02, Table 11.3, Table 11.22, Table 12.3

1. Numbers provided are not unique subjects (i.e., subjects who participated in more than one study or subjects in the Clinical Pharmacology Program who participated in multiple periods in crossover design studies are counted more than once).
2. Includes subjects treated with at least one dose of any study medication (placebo, active, or comparator) given by any route of administration.
3. All orally inhaled doses studied (regardless of inhaler used).
4. Integrated and Non-integrated Studies included adolescent and adult subjects (≥12 years of age).
5. Includes 403 subjects who were randomized to FP/SALM 250/50 BD.
6. For the two crossover studies (FFA112202 and HZA113310), only the first treatment period was used for counting subjects.
7. 135 of these subjects received the H-salt of VI

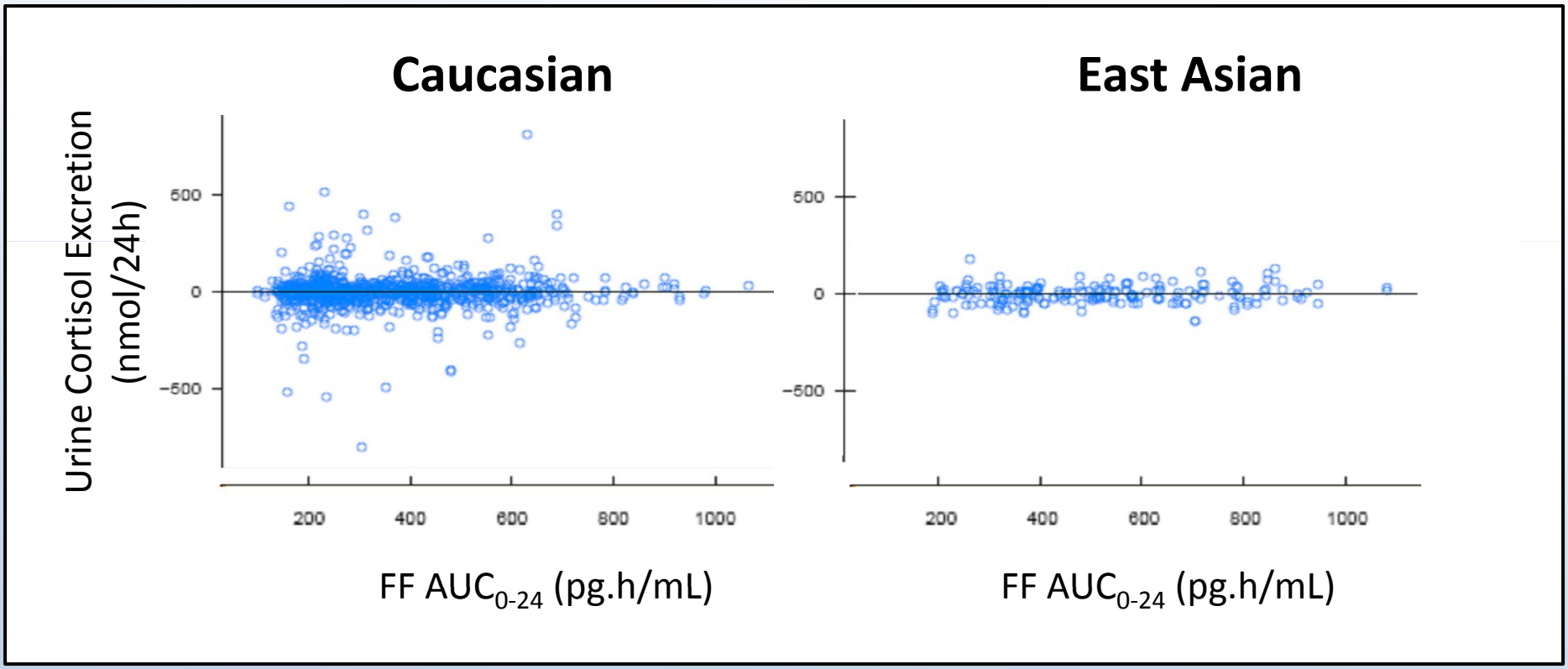
Source: Module 5.3.5.3, ISS, Table 7, pg. 50.

Heart rate population PK/PD analysis (asthma): East Asian vs. Caucasian comparison



- Higher VI exposure in East Asians was not associated with a greater effect on heart rate
- The VI C_{max} in Asian subjects with asthma is comparable to healthy subjects.

Urine cortisol excretion population PK/PD (asthma): East Asian vs. Caucasian comparison



- Higher FF exposure in East Asians was not associated with a greater effect on cortisol

Results: Primary Endpoint

Mean Annual Asthma Exacerbation Rate Per Patient

	FSC Diskus 100/50 n = 239	FP 100 mcg n = 236
Exacerbation Rate	0.449	0.529
P-Value	0.169	

Bailey, et al. *Curr Med Res Opin* 2008;24:1669-82.

Results: Secondary Endpoints

	FSC Diskus 100/50	FP 100	LS Mean Difference (95% CI)
AM PEF (L/min)			
Baseline	342	340	15.1 (5.5, 24.7)
Mean Change	15.6	1.4	
AM Pre-dose FEV_1 (L)			
Baseline	2.53	2.52	0.103 (0.041, 0.165)
Mean Change	0.045	-0.061	
Symptom-free Days, %			
Baseline	26.7	23.2	3.3 (-2.9, 9.6)
Mean Change	10.8	8.9	
Albuterol-free Days, %			
Baseline	37.9	42.1	4.5 (-1.8, 10.9)
Mean Change	10.8	5.6	

The *a priori* analysis plan required meeting the primary outcome as a prerequisite for declaring statistical significance of the secondary outcomes. As a result, the statistical results are provide only to help inform on the individual measures.

Bailey, et al. *Curr Med Res Opin* 2008;24:1669-82.

Figure 1: Risk Difference Estimates
Age Subgroup Analysis

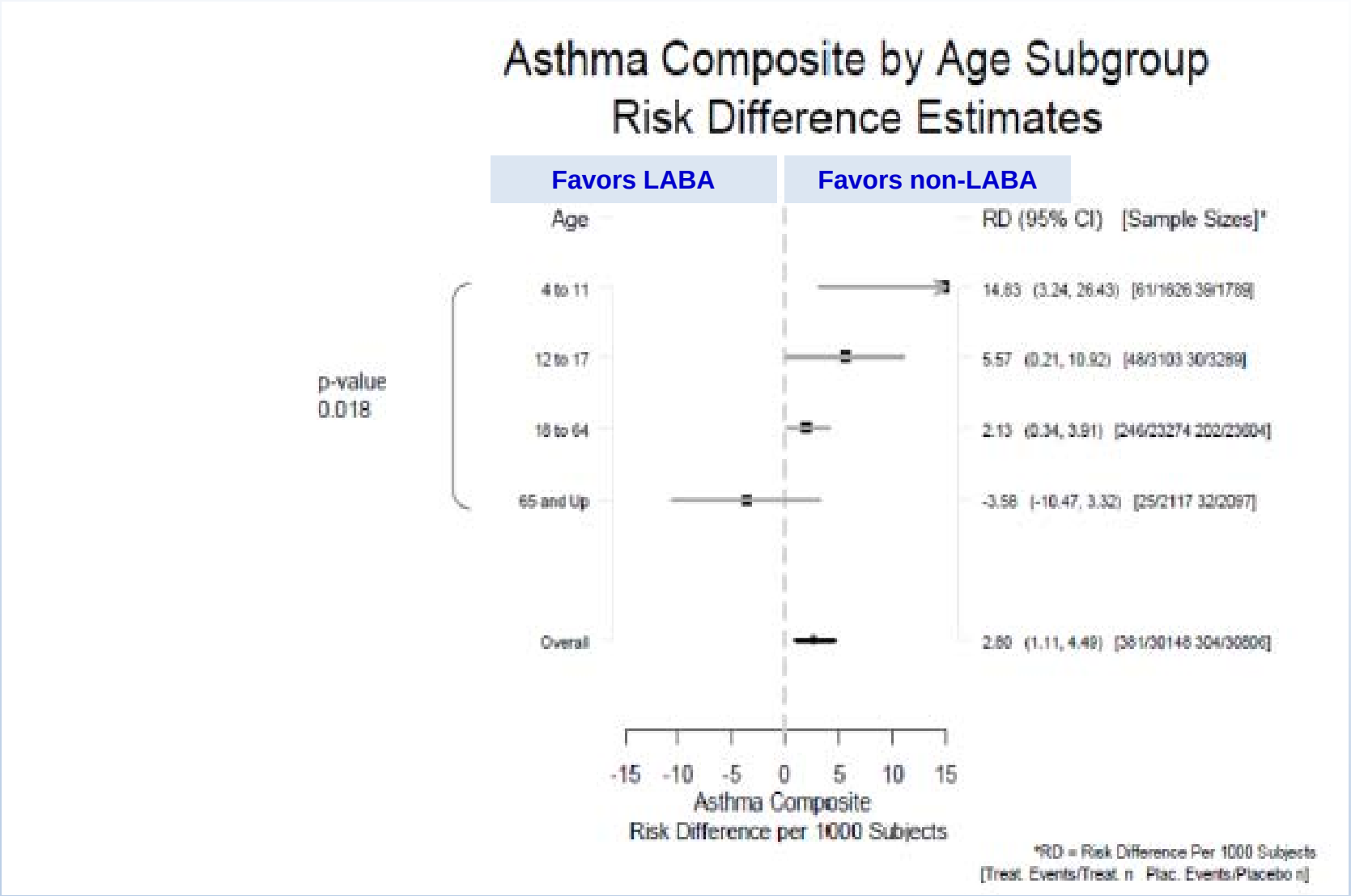
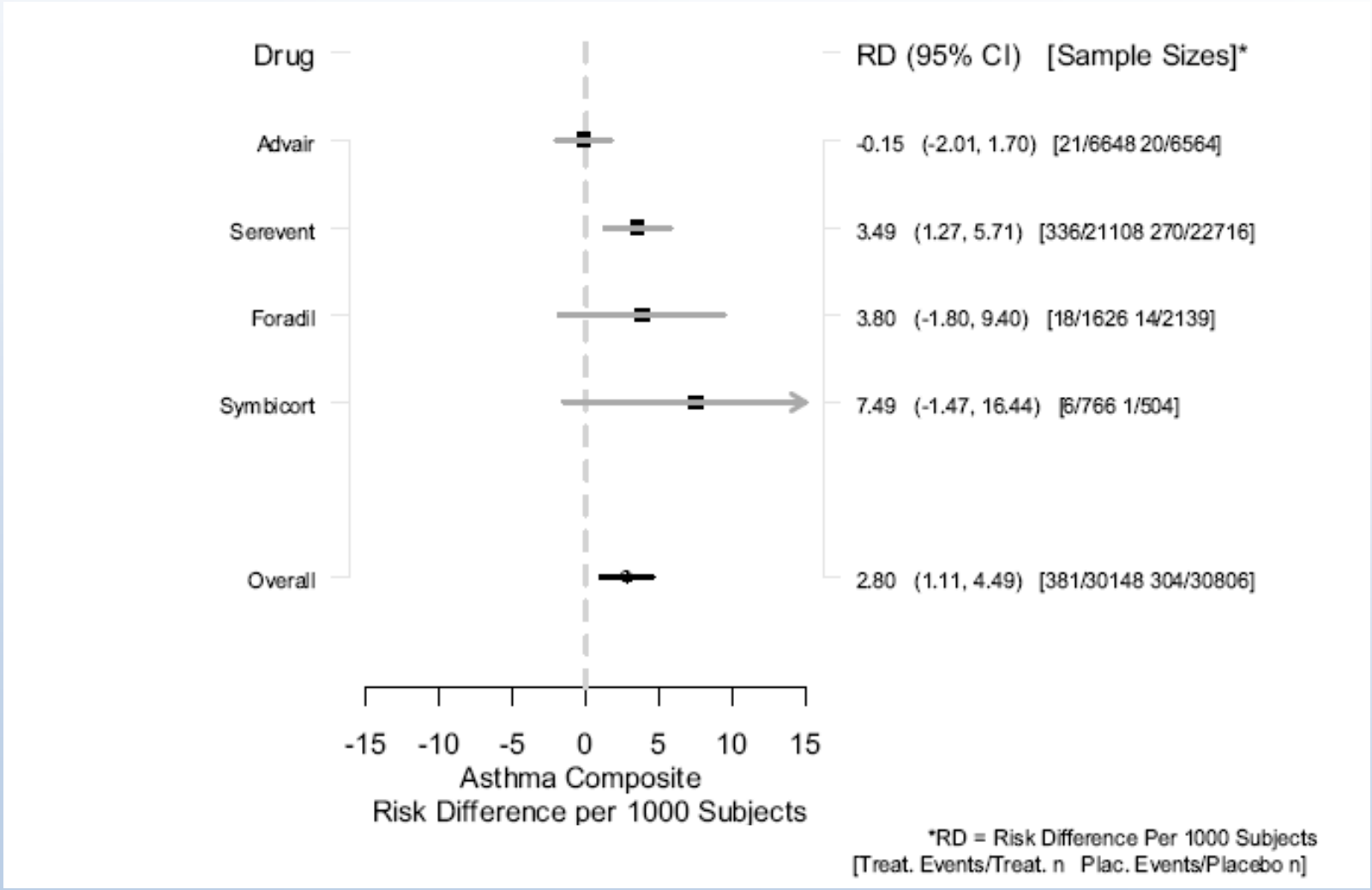
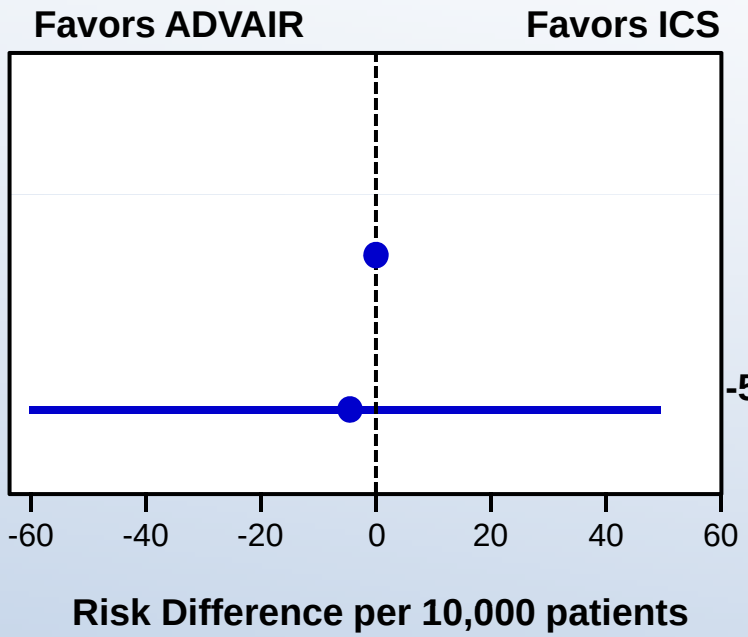


Figure 3: Risk Difference Estimates: Asthma Composite by Drug



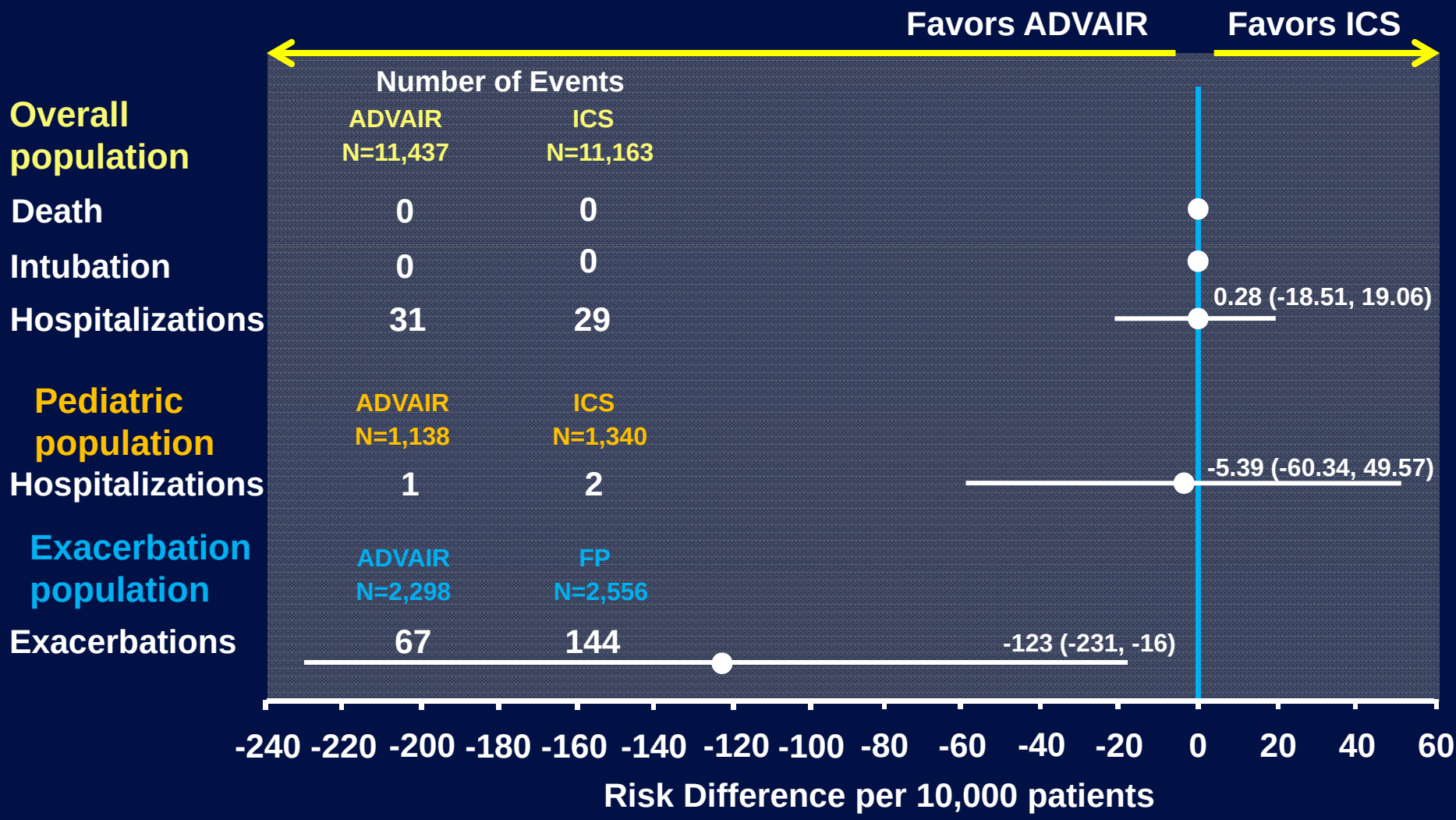
Pediatric Population
Asthma-related Death and Hospitalization with ADVAIR
2008 Analysis

	ADVAIR n	ADVAIR N	ICS n	ICS N	Risk Difference (95% CI)
Death	0	1,138	0	1,340	0 per 10,000 pts (Not estimated)
Hospitalization	1	1,138	2	1,340	-5.39 per 10,000 pts (-60.34, 49.57)



ADVAIR: Results from RCTs

Asthma-related Death, Intubation and Hospitalization and OCS-requiring Exacerbations



GSK 2008 Briefing Information; available at: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-04-GSK.pdf

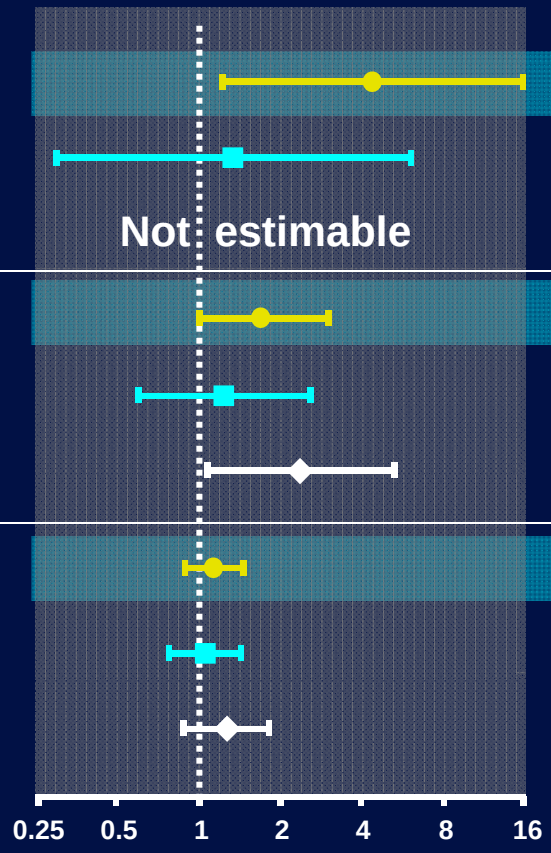
Rate of Asthma Exacerbations by Age (Study 837)

	ITT Population		12-17 years		≥18 years	
	FF 100 N=1010	FF/VI 100/25 N=1009	FF 100 N=130	FF/VI 100/25 N=151	FF 100 N=880	FF/VI 100/25 N=858
Number (events) of subjects with ≥1 asthma exacerbation	**186 (271)**	**154 (200)**	**9 (10)**	**15 (19)**	**177 (261)**	**139 (181)**
Total Exposure (Years)	*1006*	*1020*	*126.5*	*145.3*	*879.2*	*874.8*
Crude exacerbation rate per subject per year	*0.27*	*0.20*	*0.08*	*0.13*	*0.30*	*0.21*
FF/VI 100/25 vs. FF 100 Crude Ratio		0.74		1.63		0.70

Note: A separate negative binomial regression model was used for each age group with covariates of treatment, FEV_1 at baseline, sex, age and region

SEREVENT: Results from SMART

All Patients and Reported ICS Use at Baseline



	RR (95% CI)	SEREVENT n	Placebo n
Asthma-related Death	4.37 (1.25, 15.33)	13	3
	1.35 (0.30, 6.03)	4	3
	Not estimable	9	0
Asthma-related Death or Asthma-related Intubation	1.71 (1.01, 2.89)	37	22
	1.24 (0.60, 2.57)	16	13
	2.39 (1.10, 5.21)	21	9
Asthma-related Hospitalization	1.14 (0.92, 1.42)	176	153
	1.06 (0.80, 1.40)	99	93
	1.28 (0.92, 1.79)	77	60

●	Total	N=13,176 N=13,179
■	ICS	N=6,127 N=6,138
◆	Non-ICS	N=7,049 N=7,041

Adapted from Nelson H, et al. Chest 2006;129:15-26

GSK 2008 Briefing Information; available at: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-04-GSK.pdf

Baseline Asthma Characteristics in Caucasians and African Americans

	Caucasian (n=18,642)	African American (n=4685)
Peak expiratory flow (% predicted)	85%	78%
Nocturnal symptoms present	57%	64%
≥1 ER visit last 12 months	22%	41%
≥ 1 ER visit lifetime	59%	72%
≥1 hospitalization last 12 months	6%	15%
≥1 hospitalization lifetime	30%	44%
≥1 intubation for asthma lifetime	4%	8%
Baseline ICS Use	49%	38%

Nelson et al. Chest 2006;129:15-26.

Cumulative Exposure

	Placebo N=1070	FF/VI 100/25 N=2369	FF/VI 200/25 N=956	FF 100 N=2010	FF 200 N=608	VI 25 N=216
Total Exposure (n)	**1065**	**2369**	**954**	**2008**	**604**	**216**
<12 weeks, n (%)	674 (63)	388 (16)	276 (29)	493 (25)	327 (54)	152 (70)
≥12 weeks, n (%)	391 (37)	1981 (84)	678 (71)	1515 (75)	277 (46)	64 (30)
≥24 weeks, n (%)	120 (11)	1400 (59)	309 (32)	1081 (54)	180 (30)	0
≥52 weeks, n (%)	0	696 (29)	122 (13)	567 (28)	0	0
Patient Years						
Total	**215**	**1537**	**382**	**1253**	**169**	**32**